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(11) Publication number: **0 325 397 A1**

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: 89300380.6

(22) Date of filing: 17.01.89

(51) Int. Cl.4: C 07 C 127/19
C 07 C 127/17,
C 07 C 157/09,
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C 07 C 87/455, A 61 K 31/17

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(84) Designated Contracting States:
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(71) Applicant: YAMANOUCHI PHARMACEUTICAL CO. LTD.
No. 3-11 Nihonbashi-Honcho, 2-chome Chuo-ku
Tokyo (JP)

(72) Inventor: Ito, Noriki
Angel Heim 2-503 614 Ohmagi
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(74) Representative: Geering, Keith Edwin et al
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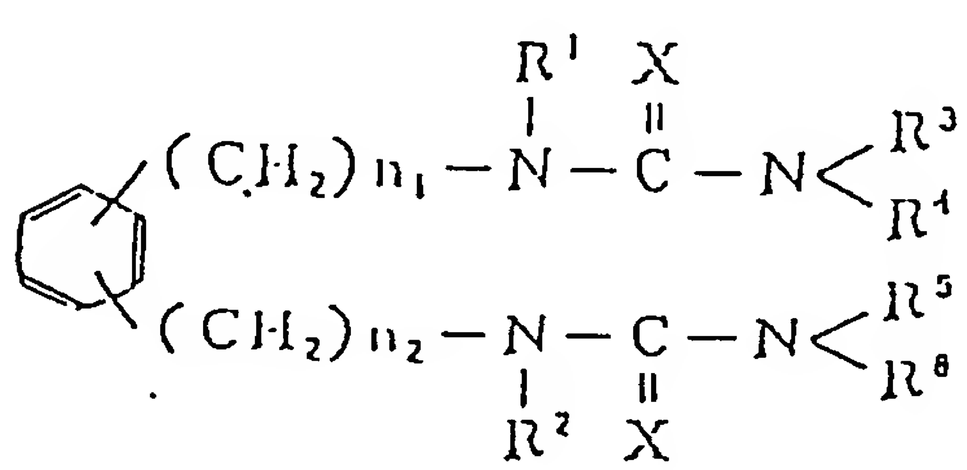
(57) Diurea Derivatives represented by the following general formula and salts thereof:



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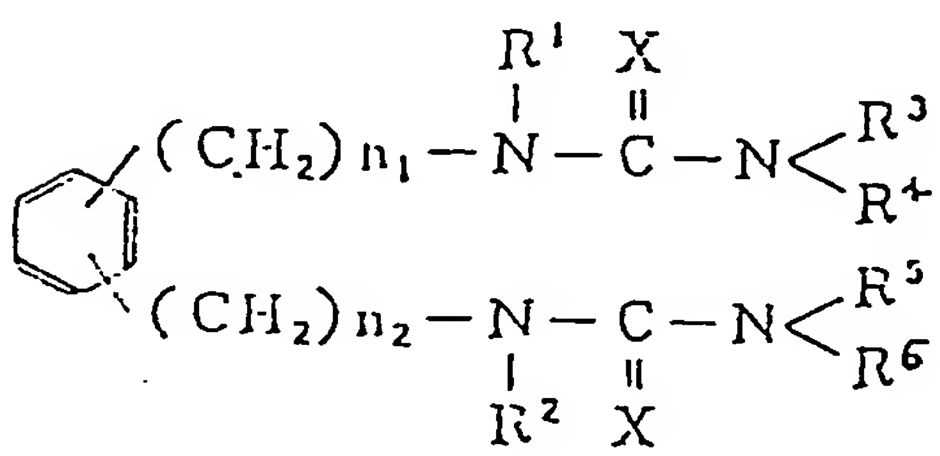
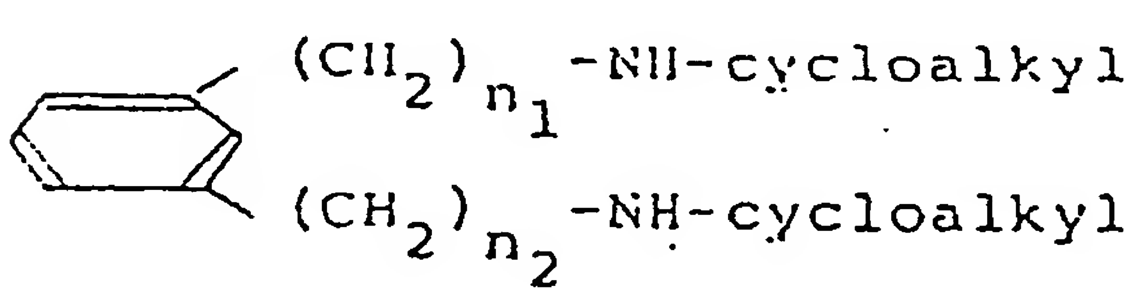


(I)

wherein
R^1 and R^2 are the same or different and selected from alkyl groups, cycloalkyl groups and lower alkyl groups substituted by cycloalkyl radical(s);
R^3, R^4, R^5 and R^6 are the same or different and selected from a hydrogen atom and lower alkyl, cycloalkyl, aralkyl, pyridyl and phenyl groups (any phenyl group optionally having one or more substituents, e.g. selected from halogen atoms and lower alkyl, halogen-substituted lower alkyl, nitro, amino, mono- and di-lower alkylamino, lower acylamino, hydroxyl, lower alkoxy and lower acyloxy radicals);
X represents an oxygen or sulfur atom; and n_1 and n_2 are the same or different integers of 1 to 6.

Preferred compounds according to the invention include those wherein R^1 and R^2 are cycloalkyl groups; R^3 and R^5 are the same or different phenyl groups; R^4 and R^6 are the same or different and selected from a hydrogen atom and C_1-C_5 alkyl, cycloalkyl, aralkyl, pyridyl, and phenyl groups; n_1 and n_2 are integers of 1 to 3.

The invention also provides intermediate compounds of the following formula :



(XIII)

wherein n_1 and n_2 are the same or different integers of 1 to 6.

It is known that deposition of cholesterol in the vascular system is an etiological cause of various diseases including coronary heart diseases. A theromatous arteriosclerosis is a form of arteriosclerosis characterized by the accumulation and hypertrophication of lipid, particularly cholesterol ester,on the medium and large arterial wall.

Recently, it has been found that acyl-coenzyme A cholesterol acyl-transferase (ACAT) catalyzes the formation of cholesterol ester. Thus, the excessive accumulation of cholesterol ester on the arterial wall is connected with increase of ACAT enzyme. Accordingly, inhibiting ACAT enzyme should decrease cholesterol esterification rate and control the formation and development of atheromatous disorder.

Cholesterols in foodstuffs are absorbed as free cholesterol, esterified by the action of ACAT enzyme, and then released into the blood in the form of chylomicron. Therefore, inhibiting ACAT enzyme should control absorption of cholesterol from foodstuffs into the intestine and re-absorption of cholesterol released into the intestine.

We have found the formula (I) compounds and their salts, which inhibit ACAT enzyme and hence can reduce the deposition of cholesterol on the arterial wall and control the absorption of cholesterol into the intestine. Compounds disclosed in U.S. -A-4,387,105 have been known as ACAT enzyme inhibitors, but are structurally different from formula (I).

Diruea compounds with the urea radical connected to phenyl via alkylene are disclosed in Japanese Patent Publication Nos. (Sho) 46-41462 and 47-29576, but these compounds are described as stabilizing agents for polyolefines and antideteriorating agents for rubber, and they are not of formula (I).

Herein, "cycloalkyl" is cyclic alkyl, preferably of 3 to 18 carbon atoms, and examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cyclododecyl, cyclotridecyl, cyclopentadecyl and the like; cyclo-alkyls having 6 to 10 carbon atoms are most preferable. "Lower alkyl" is straight or branched alkyl having 1 to 5 carbon atoms, and examples include methyl, ethyl, propyl, isopropyl,

butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl (amyl), isopentyl, tert.-pentyl, neopentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl and the like. A "lower alkyl substituted by cycloalkyl" means lower alkyl, any position of which is substituted by cycloalkyl, and examples include cyclopropyl-methyl, 2-cyclobutyllethyl, cyclopentylmethyl, 2-cyclopentylethyl, 1-cyclopentylethyl, cyclohexylmethyl, 1-cyclohexylethyl, 2-cyclohexylethyl, 1-cyclohexylpropyl, 2-cyclohexylpropyl, 3-cyclohexylpropyl, 1-cyclohexylbutyl, 2-cyclohexylbutyl, 3-cyclohexylbutyl, 4-cyclohexylbutyl, cycloheptylmethyl, 2-cycloheptylethyl, 3-cycloheptylpropyl, 4-cycloheptylbutyl, 5-cycloheptylpentyl, cyclooctylmethyl, 2-cyclooxtylethyl, 3-cyclooctylpropyl, 4-cyclooctylbutyl, cyclononylmethyl, cyclodecylmethyl, cyclododecylmethyl, cyclotridecylmethyl, 2-cyclotridecylethyl, cyclo-tetradecylmethyl, cyclopentadecylmethyl and the like.

The "alkyl" groups preferably have 1 to 10 carbon atoms, and in addition to the specific examples of lower alkyl, examples include straight or branched alkyl such as hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1-ethyl-1-methylpropyl, heptyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1,1-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, 2,4-dimethylpentyl, 3,3-dimethylpentyl, 3,4-dimethylpentyl, 1-ethylpentyl, 2-ethylpentyl, 3-ethylpentyl, 1,1,2-trimethylbutyl, 1,1,3-trimethylbutyl, 1,2,2-trimethylbutyl, 2,2,3-trimethylbutyl, 1-ethyl-1-methylbutyl, 1-ethyl-2-methylbutyl, 1-ethyl-3-methylbutyl, 1-propylbutyl, 1-isopropylbutyl, octyl, 6-methylheptyl, nonyl, 7-methylocytl, decyl, 8-methylnonyl and the like.

The "aralkyl" groups are alkyls (e.g. of 1 to 10 carbon atoms) substituted by aryl - e.g. phenyl, naphthyl, pyridyl,and the like. Representative examples include benzyl, phenethyl, phenylpropyl, phenylbutyl, phenylpentyl, phenylhexyl, naphthylmethyl, pyridylmethyl, pyridylethyl and the like. "Pyridyl" includes 2-, 3- and 4-pyridyl radicals. In addition, phenyl radicals may be substituted, e.g. by one or more groups selected from lower alkyl, halogen-substituted lower alkyl, nitro, amino, mono- and di-lower alkylamino, lower acylamino, hydroxyl, lower alkoxy and lower acyloxy radicals and halogen atoms.

Halogen atom includes fluorine, chlorine, bromine and iodine. Lower alkyl substituted by halogen atom means lower alkyl, any position of which is substituted by halogen, and examples include trichloromethyl, trifluoromethyl, 2,2,2-trichloroethyl, 2,2,2-trifluoroethyl, 2,2,2-tribromoethyl and the like. Mono- and di-lower alkylamino means amino substituted by one or two lower alkyls and examples include methylamino, ethylamino, propylamino, dimethylamino, diethylamino and the like. Lower acylamino means amino substitued by acyl having 1 to 5 carbon atoms, and examples thereof include formylamino, acetylamino, propionylamino and butylylamino. Lower alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy, tert.-butoxy, pentyloxy (amyloxy), isopentyloxy, tert.-pentyloxy, neopentyloxy, 2-methylbutoxy, 1,2-dimethylpropoxy, 1-ethylpropoxy and the like. Lower acyloxy means acyloxy having 2 to 5 carbon atoms, and examples include acetyloxy, propionyloxy butylyloxy,and the like. When a phenyl has two or more substituents they may be the same or different.

Compounds of formula (I) form salts, including acid addition salts with mineral acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric, nitric and phosphoric acids etc., and with organic acids such as formic, acetic, oxalic, citric, succinic, fumaric, maleic, malic, tartaric, methanesulfonic, and ethanesulfonic acids etc.

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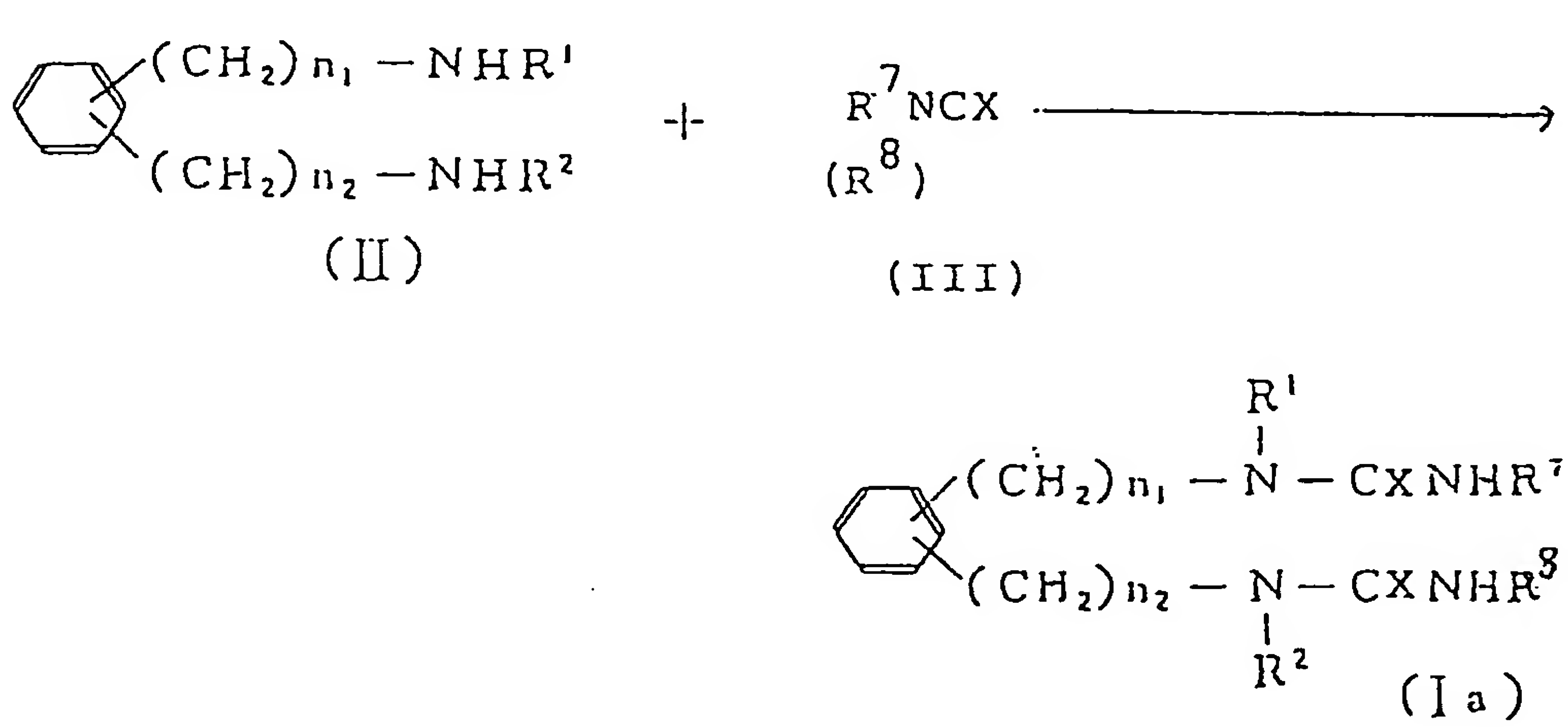

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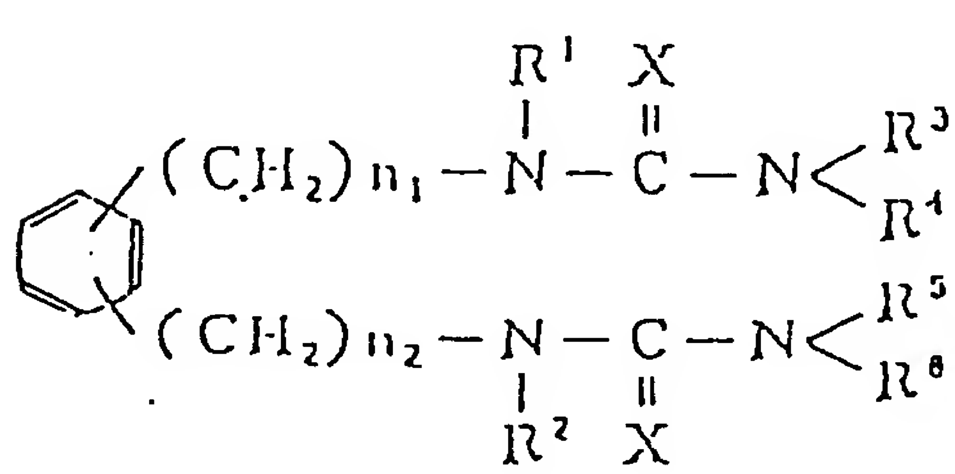

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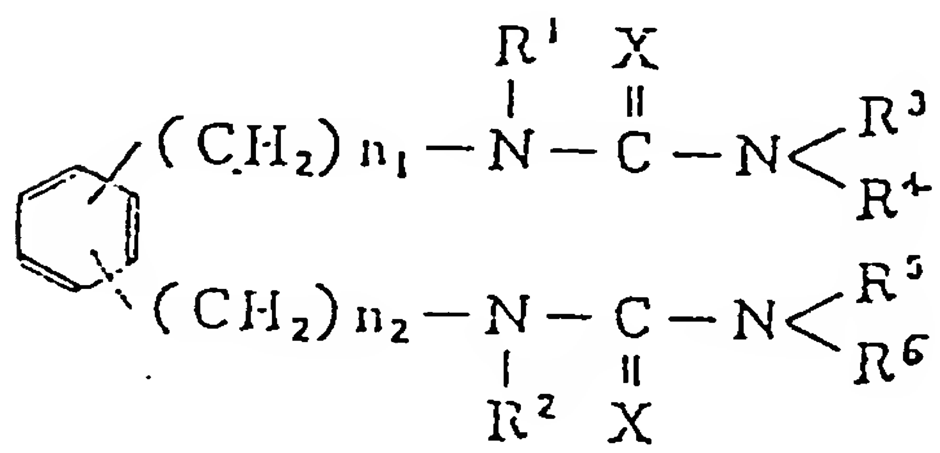

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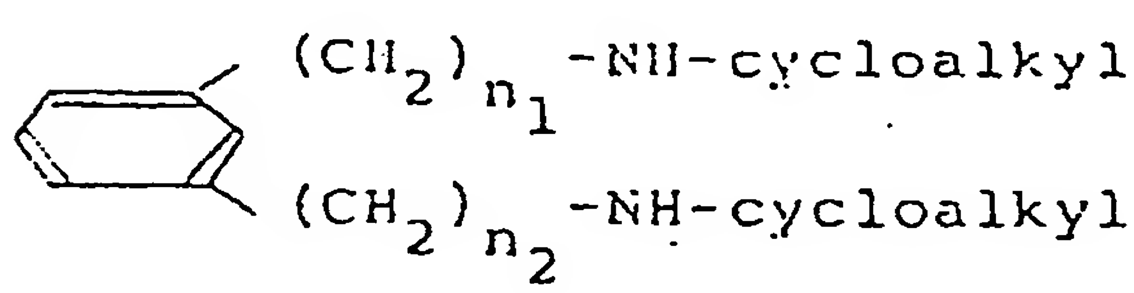

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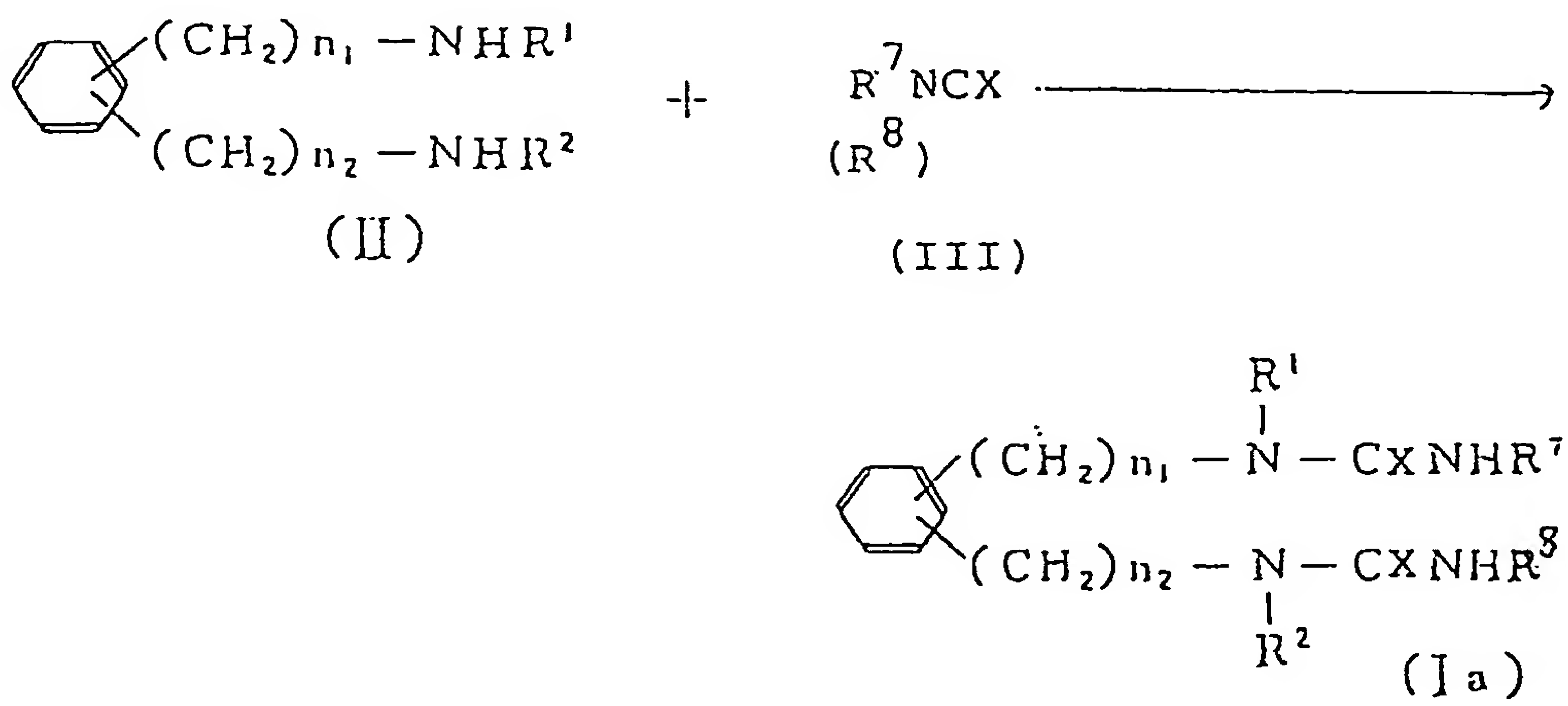

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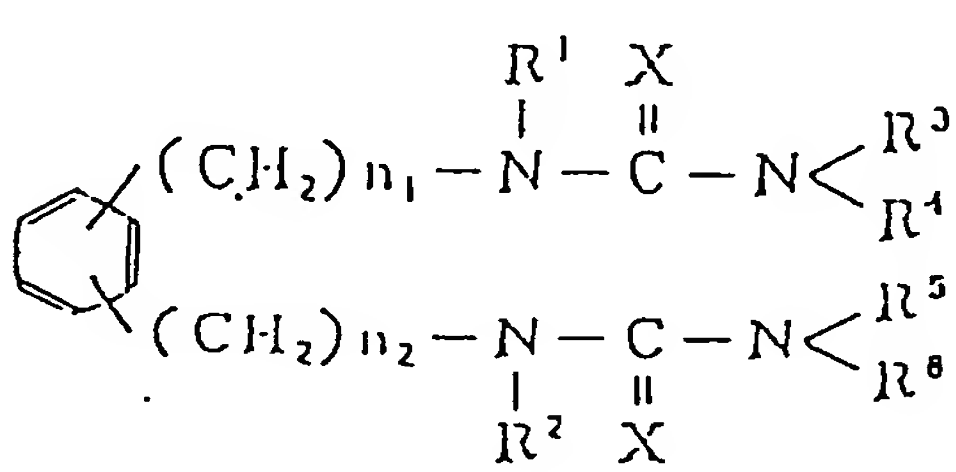

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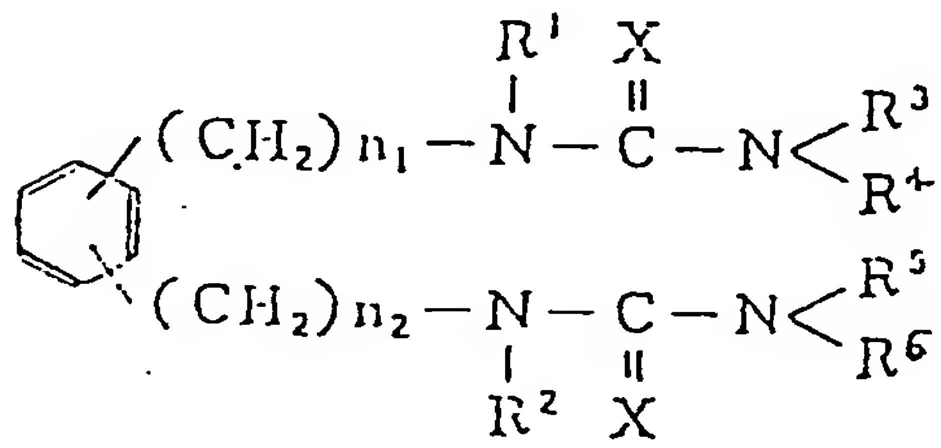

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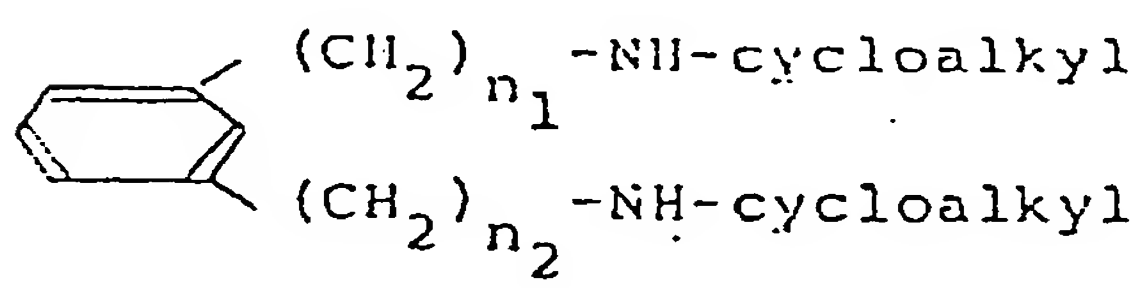

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Herein, "cycloalkyl" is cyclic alkyl, preferably of 3 to 18 carbon atoms, and examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cyclododecyl, cyclotridecyl, cyclopentadecyl and the like; cyclo-alkyls having 6 to 10 carbon atoms are most preferable. "Lower alkyl" is straight or branched alkyl having 1 to 5 carbon atoms, and examples include methyl, ethyl, propyl, isopropyl,

butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl (amyl), isopentyl, tert.-pentyl, neopentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl and the like. A "lower alkyl substituted by cycloalkyl" means lower alkyl, any position of which is substituted by cycloalkyl, and examples include cyclopropyl-methyl, 2-cyclobutyllethyl, cyclopentylmethyl, 2-cyclopentylethyl, 1-cyclopentylethyl, cyclohexylmethyl, 1-cyclohexylethyl, 2-cyclohexylethyl, 1-cyclohexylpropyl, 2-cyclohexylpropyl, 3-cyclohexylpropyl, 1-cyclohexylbutyl, 2-cyclohexylbutyl, 3-cyclohexylbutyl, 4-cyclohexylbutyl, cycloheptylmethyl, 2-cycloheptylethyl, 3-cycloheptylpropyl, 4-cycloheptylbutyl, 5-cycloheptylpentyl, cyclooctylmethyl, 2-cyclooxtylethyl, 3-cyclooctylpropyl, 4-cyclooctylbutyl, cyclononylmethyl, cyclodecylmethyl, cyclododecylmethyl, cyclotridecylmethyl, 2-cyclotridecylethyl, cyclo-tetradecylmethyl, cyclopentadecylmethyl and the like.

The "alkyl" groups preferably have 1 to 10 carbon atoms, and in addition to the specific examples of lower alkyl, examples include straight or branched alkyl such as hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1-ethyl-1-methylpropyl, heptyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1,1-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, 2,4-dimethylpentyl, 3,3-dimethylpentyl, 3,4-dimethylpentyl, 1-ethylpentyl, 2-ethylpentyl, 3-ethylpentyl, 1,1,2-trimethylbutyl, 1,1,3-trimethylbutyl, 1,2,2-trimethylbutyl, 2,2,3-trimethylbutyl, 1-ethyl-1-methylbutyl, 1-ethyl-2-methylbutyl, 1-ethyl-3-methylbutyl, 1-propylbutyl, 1-isopropylbutyl, octyl, 6-methylheptyl, nonyl, 7-methylocytl, decyl, 8-methylnonyl and the like.

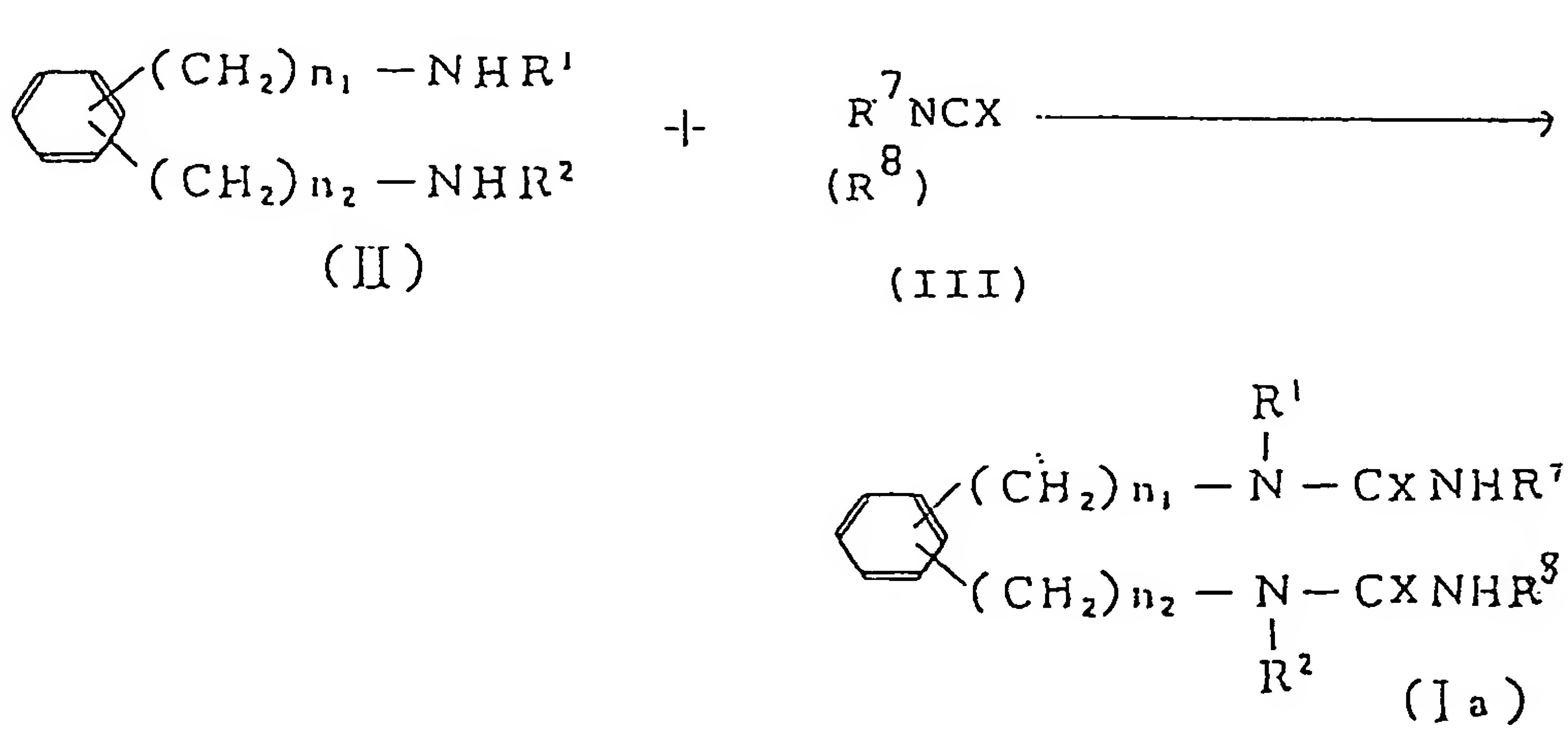
The "aralkyl" groups are alkyls (e.g. of 1 to 10 carbon atoms) substituted by aryl - e.g. phenyl, naphthyl, pyridyl,and the like. Representative examples include benzyl, phenethyl, phenylpropyl, phenylbutyl, phenylpentyl, phenylhexyl, naphthylmethyl, pyridylmethyl, pyridylethyl and the like. "Pyridyl" includes 2-, 3- and 4-pyridyl radicals. In addition, phenyl radicals may be substituted, e.g. by one or more groups selected from lower alkyl, halogen-substituted lower alkyl, nitro, amino, mono- and di-lower alkylamino, lower acylamino, hydroxyl, lower alkoxy and lower acyloxy radicals and halogen atoms.

Halogen atom includes fluorine, chlorine, bromine and iodine. Lower alkyl substituted by halogen atom means lower alkyl, any position of which is substituted by halogen, and examples include trichloromethyl, trifluoromethyl, 2,2,2-trichloroethyl, 2,2,2-trifluoroethyl, 2,2,2-tribromoethyl and the like. Mono- and di-lower alkylamino means amino substituted by one or two lower alkyls and examples include methylamino, ethylamino, propylamino, dimethylamino, diethylamino and the like. Lower acylamino means amino substitued by acyl having 1 to 5 carbon atoms, and examples thereof include formylamino, acetylamino, propionylamino and butylylamino. Lower alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy, tert.-butoxy, pentyloxy (amyloxy), isopentyloxy, tert.-pentyloxy, neopentyloxy, 2-methylbutoxy, 1,2-dimethylpropoxy, 1-ethylpropoxy and the like. Lower acyloxy means acyloxy having 2 to 5 carbon atoms, and examples include acetyloxy, propionyloxy butylyloxy,and the like. When a phenyl has two or more substituents they may be the same or different.

Compounds of formula (I) form salts, including acid addition salts with mineral acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric, nitric and phosphoric acids etc., and with organic acids such as formic, acetic, oxalic, citric, succinic, fumaric, maleic, malic, tartaric, methanesulfonic, and ethanesulfonic acids etc.

Compounds according to the present invention may be prepared by various methods, e.g. :

Process 1

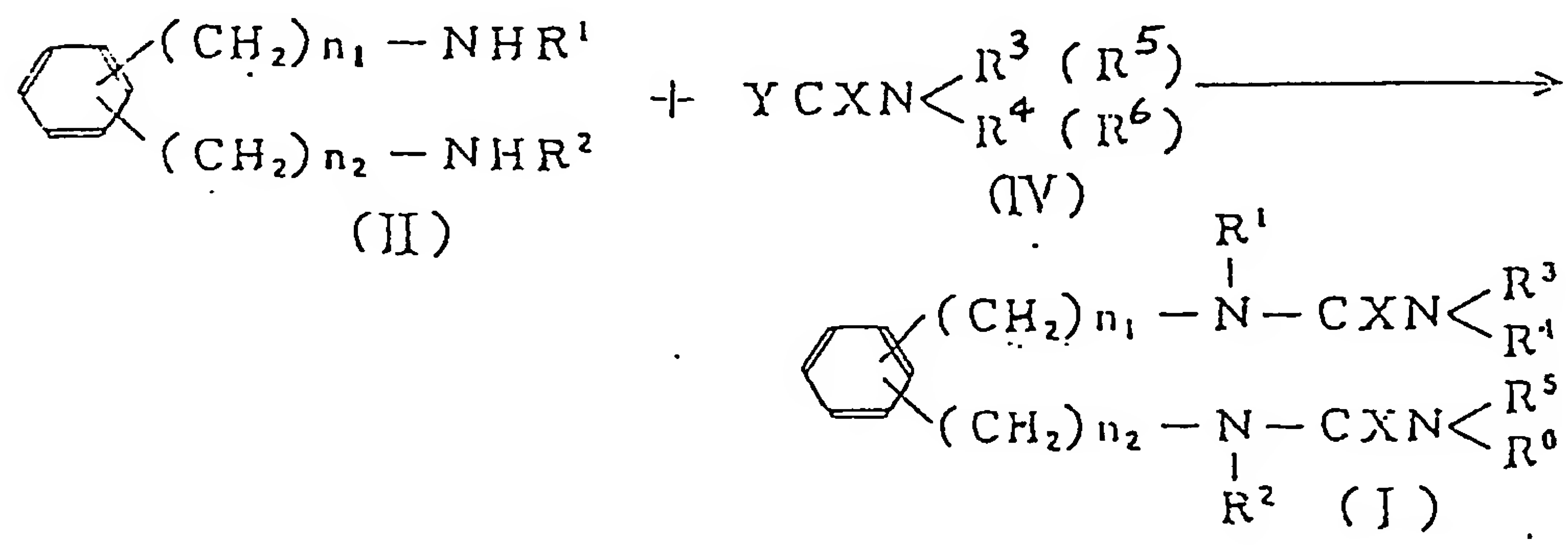


wherein

R^7 and R^8 are the same or different and selected from a hydrogen atom and cycloalkyl, aralkyl, pyridyl and phenyl groups (where phenyl may be substituted e.g. by one or more of lower alkyl, halogen, nitro, amino, mono- and di-lower alkylamino, lower acylamino, hydroxyl, lower alkoxy and lower acyloxy);and R^1, R^2, X, n_1 and n_2 are as previously defined.

Compounds of formula (I_a) may be obtained by reacting diamino compound (II) with one or more isocyanate compounds (III). Isocyanate compound (III) may be used in an amount of 2 or more moles per mole of compound (II). The reaction may be carried out in an inert solvent, such as N,N-dimethylformamide, pyridine, benzene, toluene, dioxane, tetrahydrofuran, ether, chloroform, dichloromethane, dichloroethane, n-hexane etc. at room temperature or with heating.

Process 2

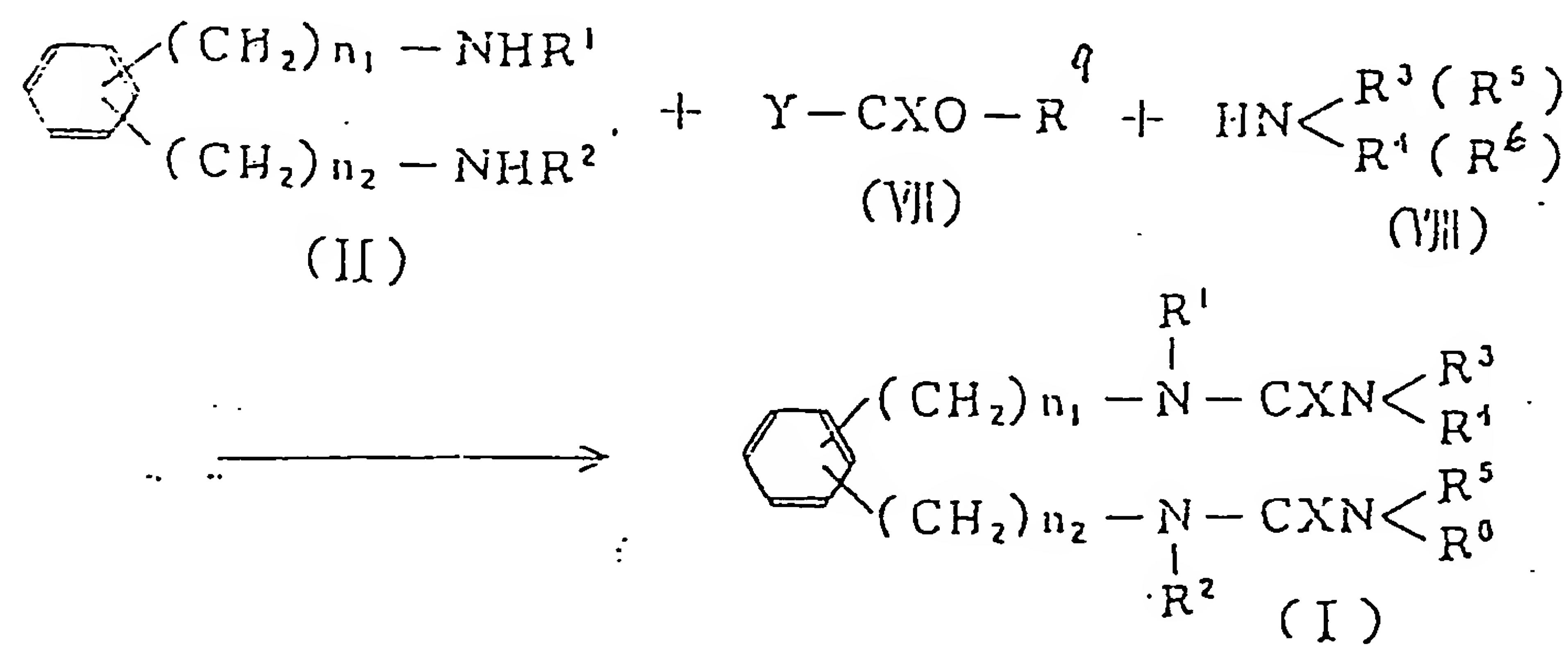


wherein

Y represents a halogen atom, and R^1, R^2, R^3, R^4, R^5, R^6, X, n_1 and n_2 are as defined above.

Compounds of formula (I) may be prepared by reacting amino compound (II) with halogen compound(s) (IV). The reaction may be carried out by reacting amino compound (II) with 2 or more moles of halogen compound (IV) in an inert solvent, such as N,N-dimethylformamide, benzene, toluene, dioxane, tetrahydrofuran, ether, chloroform, dichloromethane, dichloroethane, n-hexane etc. The reaction temperature may be suitably controlled according to the kind of starting compound and the solvent, but may be conventionally set at room temperatur or above.

Process 3



wherein

R^1, R^2, R^3, R^4, R^5, R^6, X, Y, n_1 and n_2 are as defined above, and

R^9 represents a lower alkyl or phenyl group.

Compounds of formula (I) may be obtained by reacting amino compound(s) (VIII) with carbon halide compound (VII) to give carbamic acid ester, and then reacting the resulting compound with compound (II).

Examples of carbon halide compound (VII) include isobutylcarbon chloride, methylcarbon chloride, ethylcarbon bromide, phenylcarbon chloride,and the like. In addition, in order to promote the reaction, it is advantageous to effect the reaction in the presence of base such as potassium carbonate, sodium carbonate, sodium hydroxyide, potassium hydroxide, triethylamine, N,N-dimethylanilline and the like. Suitable reaction solvents include inert solvents such as N,N-dimethylformamide, chloroform, benzene, toluene, xylene, dioxane, ether, tetrahydrofuran, chloroform, dichloromethane, dichloroethane and the like. When amino compound (II) is reacted with carbon halide compound, the reaction temperature may be set below or at room temperature, whereas the temperature for the reaction between carbamic acid ester thus obtained and compound (II) may be set above or at room temperature.

Other methods for preparing the desired compounds include converting one substituent into another. Thus among the substituents of a phenyl radical, one may replace an amino radical with a mono- or di-alkylamino or acylamino radical, a nitro radical with an amino radical, or an acyloxy radical with a hydroxyl radical.

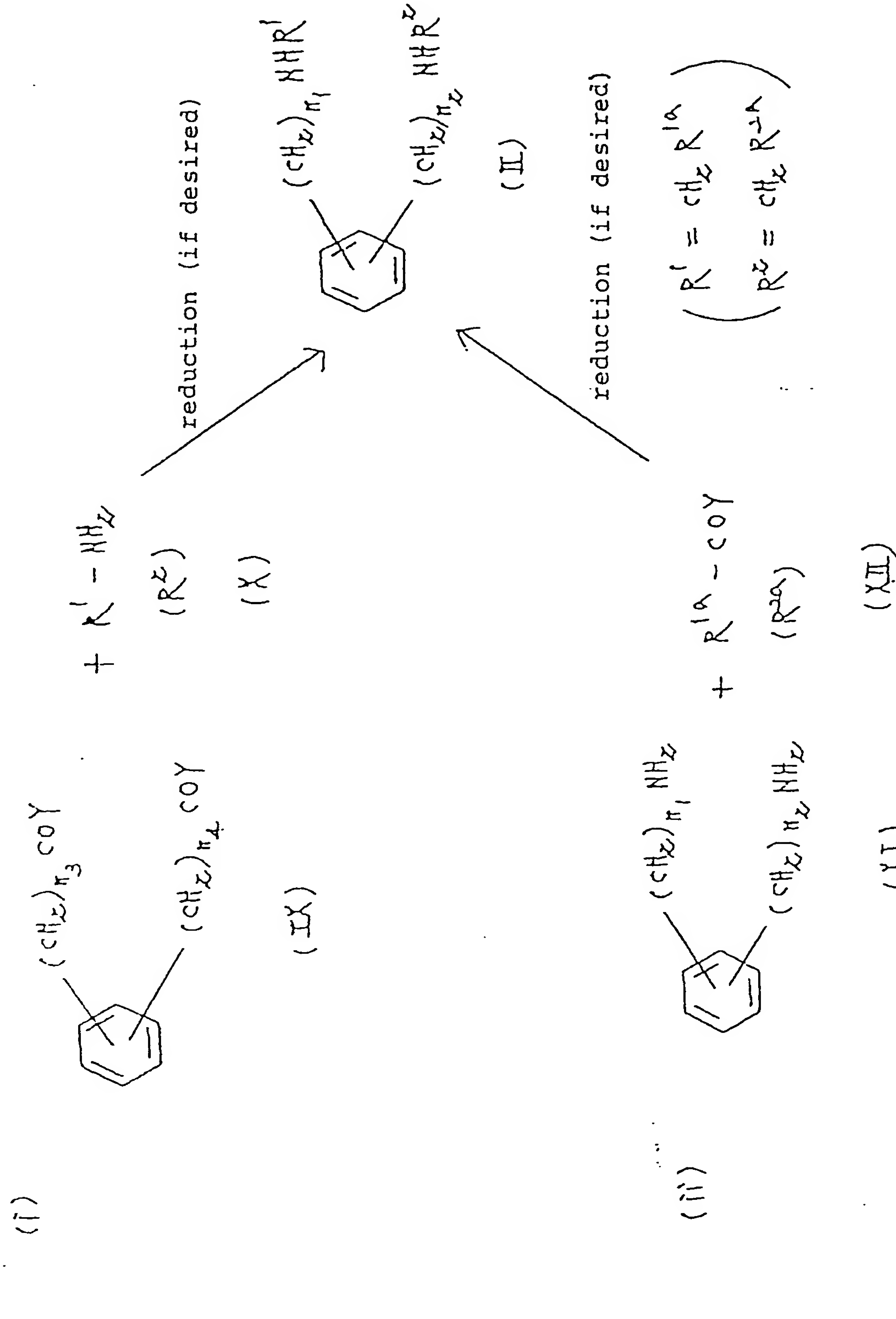
To replace aromatic amino with aromatic (mono- or di-) alkylamino, although conventional alkylation can be employed, reductive amination is preferable, in which the resulting compound is reacted with aldehyde to give imine, which is then reduced to amine.

For the reduction of imine, it is preferable to employ a catalyst such as palladium-carbon, platinum oxide and the like, or metal hydride such as sodium cyanoborohydride, lithium cyanoborohydride and the like.

For the replacement of aromatic nitro with aromatic amino, conventional catalytic reduction may be employed. Palladium-carbon, Raneynickel, platinum and the like are used as catalysts.

Aromatic amino may be replaced by acylamino by conventional acylation, wherein active derivative such as anhydride, halide, mixed acid anhydride of lower alkyl carboxylic acid are used.

Substitution of acyloxy by hydroxy may be readily effected by using a base (for example, sodium hydroxide, potassium hydroxide, sodium carbonate and the like). Diamino compound (II) used as a starting compound in the present invention may be prepared as follows:



wherein

Y is a hydrogen or halogen atom, n_3 and n_4 are the same or different and selected from 0 and integers of 1 to 5, and n_1, n_2, R^1 and R^2 are as defined above. Phenylenediamine derivative (II_a) may be obtained (i) by reacting carbonyl compound (IX) with amino compound (X) and then, if desired, reducing or (ii) by reacting diamine compound (XI) with carbonyl compound (XII) and then, if desired, reducing.
The temperature for reaction of compounds (IX) and (X), or of compounds (XI) and (XII) may be set under ice-cooling or at room temperature. Benzene, hexane, toluene, xylene, dichloromethane, chloroform, N,N-dimehtylformamide and the like may be used as reaction solvent.

To accelerate the reaction,it is preferable to add organic base such as trimethylamine,triethylamine or the like or inorganic base such as sodium carbonate, sodium hydrogen carbonate or the like.
The reduction may be effected using aluminium lithium hydride, diisobutylaluminium hydride, bis(2-methoxyethoxy) aluminium sodium hydride, tetrahydrofuran-borate complex, dimethylsulfide-borate complex or the like, in a solvent such as toluene, benzene, xylene, tetrahydrofuran, dioxane, ether, etc. The reaction may be conducted under heating or ice-cooling or at room temperature. The compound (I) or (II) of the present invention thus obtained may be separated and purified in free form or salt form by salt-forming or de-salting by conventional methods and extraction, crystallization, chromatography, etc. The compounds of formula (I) and their salts inhibit ACAT enzyme, and thereby control the accumulation of cholesterol ester on the smooth muscle of arterial walls.

Compared with known anti-lipidemia agents, the present compounds control the absorption of cholesterol into the intestine and accelerate catabolic excretion of cholesterol in the liver, and thereby lower the cholesterol level in blood. The present compounds reduce the accumulation and storage of cholesterol on the arterial wall, and thereby control the formation or development of atheromatous arteriosclerosis.

As can be seen from animal tests, compounds (I) and their salts lower total cholesterol and low density lipoprotein (LDL) in blood; they thus lower lipid level in blood and are useful for prevention and treatment of various diseases related to arteriosclerosis such as cerebral infarction, temporary ischemic spasm, angina pectrosis, peripheral thrombus and ileus.

Effects of the present compounds are verified as follows:

(i) ACAT enzyme inhibiting activity

Inhibiting activity against acyl CoA : cholesterol acyltransferase (ACAT) activity of rabbit's liver microsome
According to Heider's method [J.G. Heider et al., J. of Lipid Res. Vol. 24, 1127-34 (1983)], rabbit's liver microsome was treated to obtain an enzyme fraction.
To 0.154M of phosphoric acid buffer solution (pH 7.4), 2mM of dithiothreitol, 36μM of bovine serum albumin and 10 to 100μg of microsome fraction, liposome prepared by Suckling's method [K.E. Suckling et al., FEBS Letters, Vol. 151, No. 1, 111-116 (1983)] was added to give 20% v/v. To this, 2% v/v of dimethylsulfoxide solution of each concentration of compound to be tested was added and the mixture was heated for 5 minutes at of 37°C. Then 36μM oleoyl CoA containing 1-^{14}C-oleoyl CoA was added and the whole mixture was heated for 10 minutes at 37°C. The reaction was stopped by adding chloroform/methanol (=2/1). Upon stirring, cholesterol oleate extracted into the chloroform layer was separated by thin layer chromatography and the radioactivity was then determined as ACAT activity.

Table 1

Compound to be tested	Inhibiting activity against ACAT activity: IC (M) 50%
Compound of Example 1	1.8×10^{-8}
Compound of Example 49	$4.4. \times 10^{-8}$

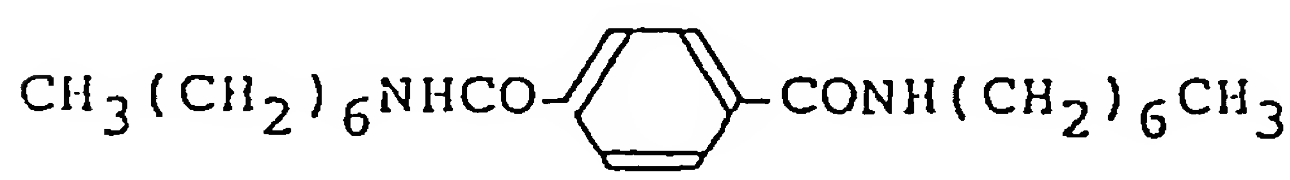
(ii) Action for lowering lipid level in blood

To a male rat (5 weeks old, Sprague-Dawley), bait containing 1.5% of cholesterol and 0.5% of bile acid was provided for 7 days, and for the last 5 days compound (I) suspended in 0.5% aqueous methylcellulose was orally administered via Sonde once per day. Two hours after the last administration, blood was gathered under etherization, and the total amount of blood cholesterol was determined according to Siedel's method [Siedel, J., et al., J. Clin. Chem. Clin. Biochem. 19, 838 (1981)] and the amount of HDL-cholesterol in blood was determined according to Ishikawa's method [Ischikawa, T.T., et al., Lipids 11, 628 (1976)]. According to these methods, compounds of formula (I) and salts thereof, administered at a dosage of 3-30 mg/Kg effectively reduced the blood cholesterol level of the male rats.

Medicaments containing (e.g. as a major component) compounds of formula (I) or salts thereof may be prepared using normal pharmaceutical carriers and excipients in conventional ways. The types of administration may include oral administration of tablets, pills, capsules, granules, powders, solutions and the

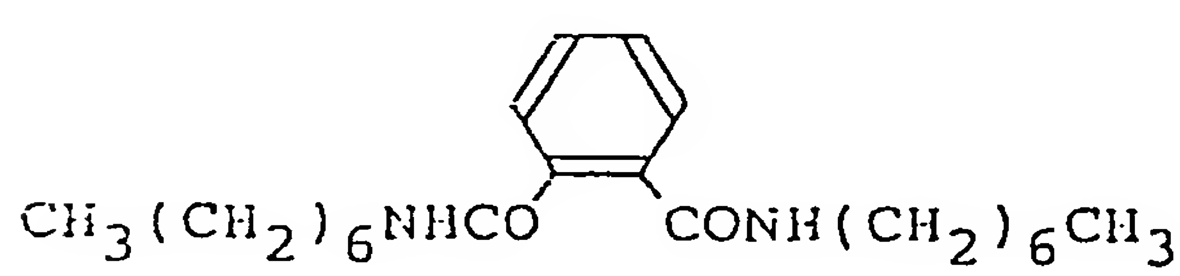
like, or parenteral administration by intravenous injection and intramuscular injection, suppositories and the like.
The dosage may be suitably determined depending upon the condition and age and sex of the subject and in the case of conventional oral administration the dosage is e.g. 50 to 500 mg per day for an adult in one or two to four doses. The following Examples and Reference Examples illustrate the present invention in more detail, and in them ^{1}H-NMR means hydrogen nuclear magnetic resonance spectrum, mp denotes melting point, Mass represents mass analysis value, and IR refers to infra red absorption spectrum. The Reference Examples show preparation of various intermediate compounds for preparation of formula (I) compounds and salts, including some intermediates of formula (XIII) above which are part of the invention.

Reference Example 1



To a mixture of 4.6 g heptylamine, 4.04 g triethylamine and 30 ml methylene dichloride, was added with stirring 4.06 g terephthaloyl chloride under ice cooling. Stirring was continued at room temperature for two hours, and the solid which separated out was collected by filtration, washed with methylene dichloride and water in that order, and dried, giving 6.5 g of N,N'-diheptylterephthalamide.
(i) ^{1}H-NMR ($CDCl_3$, δ ppm)
0.88 (6H, t), 3.28 (4H, q), 7.88 (4H, s)
(ii) Mass (EI) m/z 160 (M^+)
The following compound was prepared in much the same manner as in Reference Example 1.

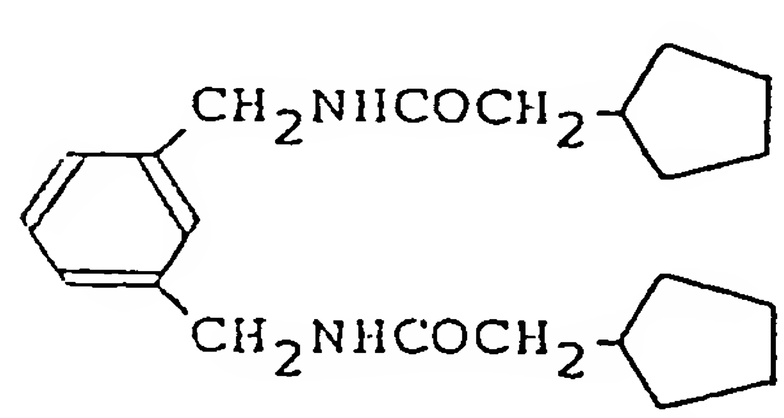
Reference Example 2



N,N'-Diheptylphthalamide

(i) ^{1}H-NMR ($CDCl_3$, δ ppm)
0.90 (6H, t), 3.38 (4H, q), 7.52 (4H, m)
(ii) Mass (EI) m/z 360 (m^+)

Reference Example 3



To a mixture of 1.36 g m-xylylenediamine, 2.4 g triethylamine and 50 ml methylene dichloride, was added with stirring 3.2 g cyclopentylacetyl chloride under ice cooling. Stirring was continued at room temperature for two

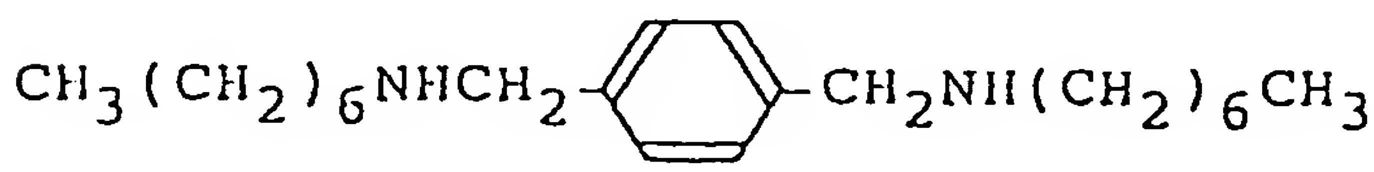
hours, and the solid which separated out was collected by filtration, washed with methylene dichloride and water in that order and dried, giving 2 g of m-xylylene-cyclopentylmethyldiamide.

(i) ^{1}H-NMR ($CDCl_3$, δ ppm)

4.40 (4H, d), 6.84-7.44 (4H, m)

(ii) Mass (FAB) m/z 357 ($M^+ + 1$)

Reference Example 4 (Starting material in Example 14)



To a mixture of 3.6 g N,N′-diheptylterephthalamide obtained in Example 1 and 60 ml toluene, was added dropwise 15.6 ml of a 70% solution of bis(2-methoxyethoxy)aluminum hydride in toluene. After heating under reflux for three hours, the reaction mixture was treated with 30 ml of 2.5N aqueous caustic soda solution under ice cooling, and the toluene layer separated was washed with saturated aqueous sodium chloride and dried over a drying agent. Distilling off the solvent from the dried solution gave 3.24 g of N,N′-diheptyl-p-xylylenediamine.

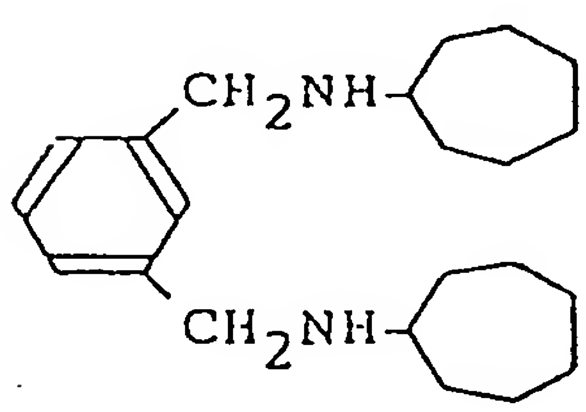
(i) ^{1}H-NMR ($CDCl_3$, δ ppm)

0.88 (6H, t), 3.76 (4H, s), 7.26 (4H, s)

(ii) Mass (EI) m/z 332 (M^+)

The following two compounds were prepared in much the same manner as in Reference Example 4.

Reference Example 5 (Starting material for Example 1 and other Examples. See also Reference Example 11)



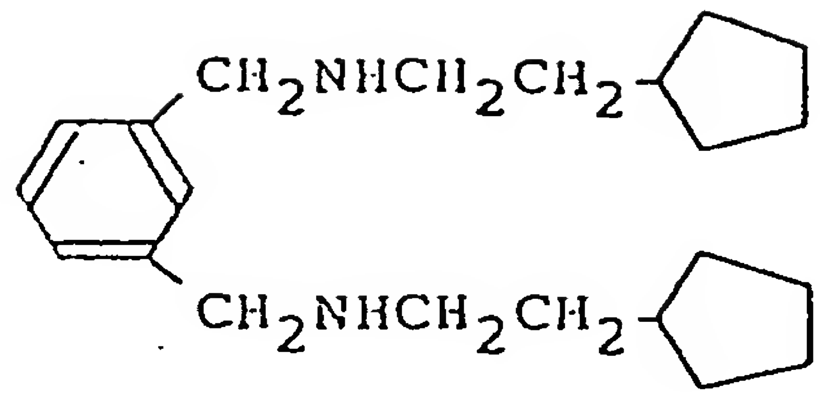
N,N'-Dicycloheptyl-m-xylylenediamine

(i) ^{1}H-NMR ($CDCl_3$, δ ppm)

3.74 (4H, s)

(ii) Mass (EI) m/z 328 (M^+)

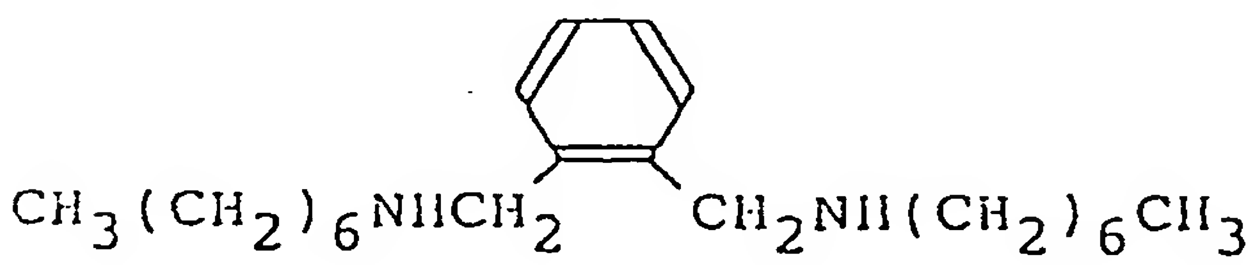
Reference Example 6 (Starting material in Example 12)



m-Xylylene-cylcopentylethyldiamine

(i) ^{1}H-NMR ($CDCl_3$, δ ppm)
2.64 (4H, t), 3.80 (4H, s)
(ii) Mass (FAB) m/z 329 ($M^+ + 1$)

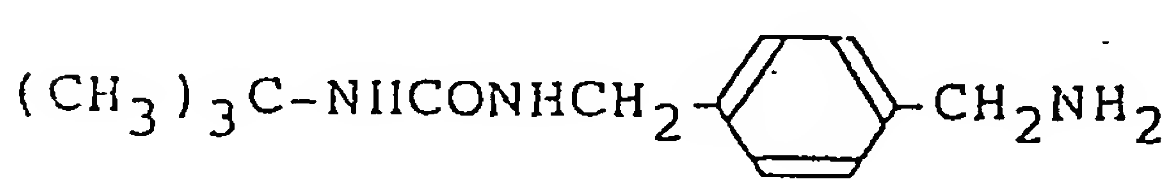
Reference Example 7 (Starting material for Example 13)



To a 1M solution of borane-tetrahydrofuran complex (24 ml) was added dropwise under ice cooling a 5 ml tetrahydrofuran solution containing 3.6 g of N,N'-diheptylphthalamide obtained in Reference Example 2 under an argon gas stream, and the mixture was warmed up slowly and then heated under reflux for one hour. After cooling, 2 ml methanol was added dropwise under ice cooling, and the mixture was heated under reflux for 30 minutes. After cooling in ice, 4.24 ml concentrated hydrochloric acid was added, and the mixture was again heated under reflux for 30 minutes. The solvent was distilled off under reduced pressure, and the residue was basified by addition of aqueous caustic soda and extracted with chloroform. After distilling off the chloroform from the extract, the residue was purified by silica gel column chromatography, giving 0.43 g of N,N'-diheptyl-o-xylylenediamine.

(i) ^{1}H-NMR ($CDCl_3$, δ ppm)
0.88 (6H, t), 2.64 (4H, t), 3.80 (4H, s)
(ii) Mass (CI) m/z 333 ($M^+ + 1$)

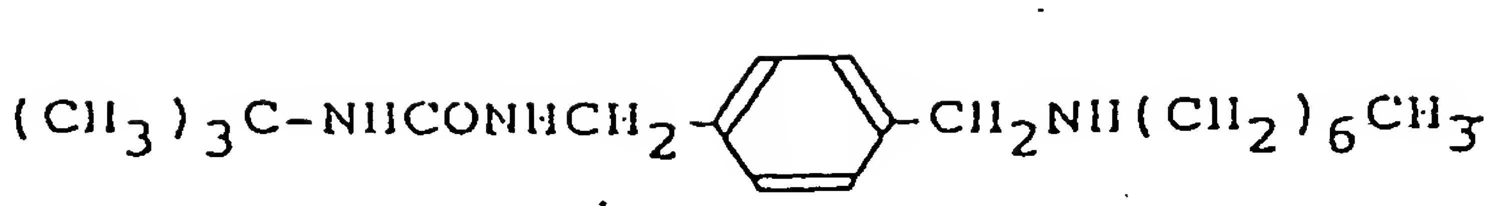
Reference Example 8



To a solution of 2.7 g p-xylylenediamine in 100 ml methylene dichloride, was added slowly with stirring 10 ml of a n-hexane solution containing 990 mg t-butyl isocyanate under ice cooling. Stirring was continued at room temperature for two hours, the solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography, giving 1 g of 4-(3-t-butylureidomethyl)-1-aminomethylbenzene.

(i) ^{1}H-NMR ($CDCl_3$, δ ppm)
1.32 (9H, s), 3.84 (2H, s), 7.24 (4H, s)
(ii) Mass (EI) m/z 235 (M^+)

Reference Example 9 (Starting material in Example 3)



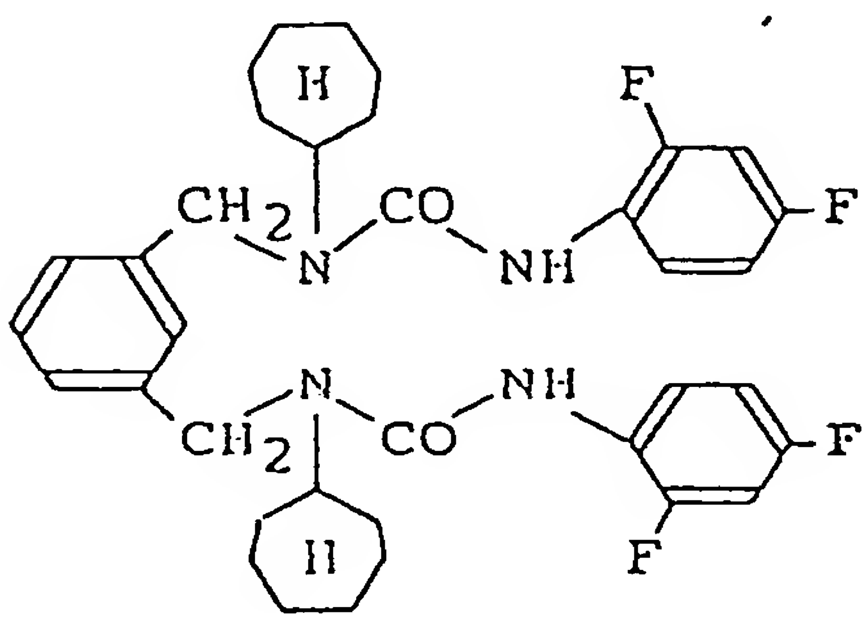
A mixture of 0.97 g 4-(3-t-butylureidomethyl)-1-aminomethylbenzene obtained in Reference Example 8, 0.57 g anhydrous potassium carbonate and 20 ml dimethylformamide was stirred at room temperature for 30 minutes, 0.93 g 1-iodeheptane was added, and stirring was continued at room temperature for an additional three hours. After distilling off the solvent under reduced presure, the residue was extracted with chloroform, and the extract was washed with water. The chloroform was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography, giving 0.65 g g of 4-(3-t-butylureido-methyl)-1-(N-heptylaminomethyl)benzene.

(i) ^{1}H-NMR ($CDCl_3$, δ ppm)

0.88 (3H, t), 2.60 (2H, t), 3.72 (2H, s)

(ii) Mass (EI) m/z 333 (M^+)

Example 1



To a solution of 1 g N,N′-dicycloheptyl-m-xylylenediamine in 50 ml n-hexane, was added dropwise with stirring 5 ml of a n-hexanesolution containing 1 g 2,4-difluorophenyl isocyanate under ice cooling. Stirring was continued at room temperature for two hours, the solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography and then recrystallized from isopropanol, giving 1.6 g of 1,3-bis[[1-cycloheptyl-3-(2,4-difluorophenyl)ureido]methyl]benzene.

(i) M.p. 71-72°C

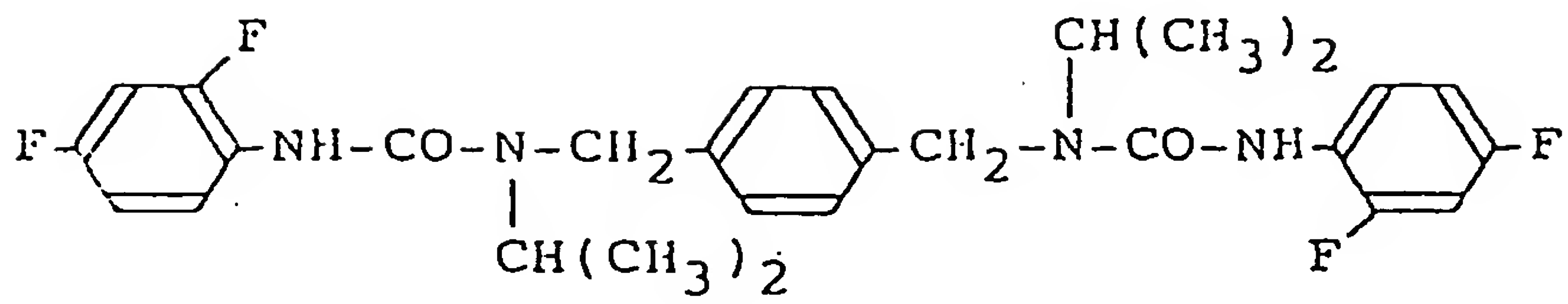
(ii) Mass (FAB) m/z 639 ($M^+ + 1$)

(iii) Elemental analysis ($C_{36}H_{42}N_4O_2F_4$)

	C	H	N
Calcd. (%)	67.69	6.63	8.77
Found (%)	67.68	6.71	8.74

The following four compounds were prepared in much the same manner as in Example 1.

Example 2

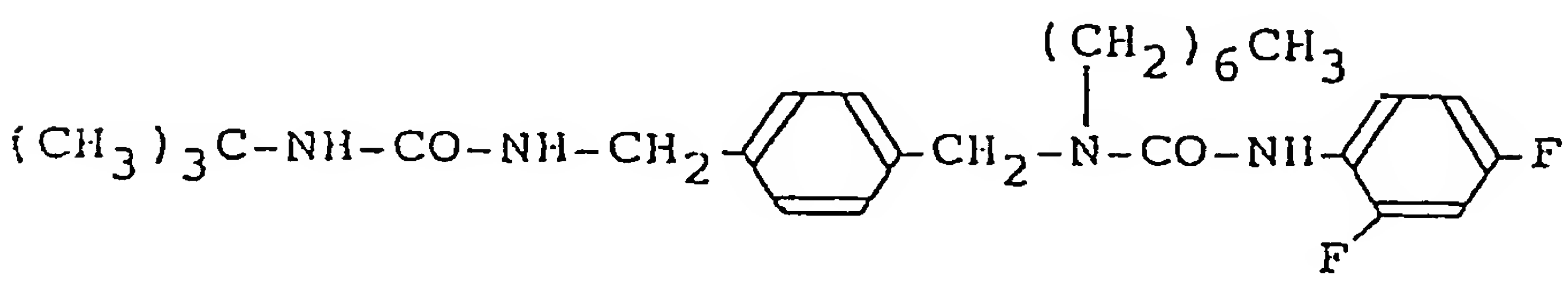


1,4-Bis[[3-(2,4-difluorophenyl)-1-isopropylureido]-methyl]benzene

(i) M.p. 167-168°C
(ii) Mass (FAB) m/z 531 ($M^+ + 1$)
(iii) Elemental analysis ($C_{28}H_{30}N_4O_2F_4$)

	C	H	N
Calcd. (%)	66.39	5.70	10.56
Found (%)	63.40	5.93	10.42

Example 3

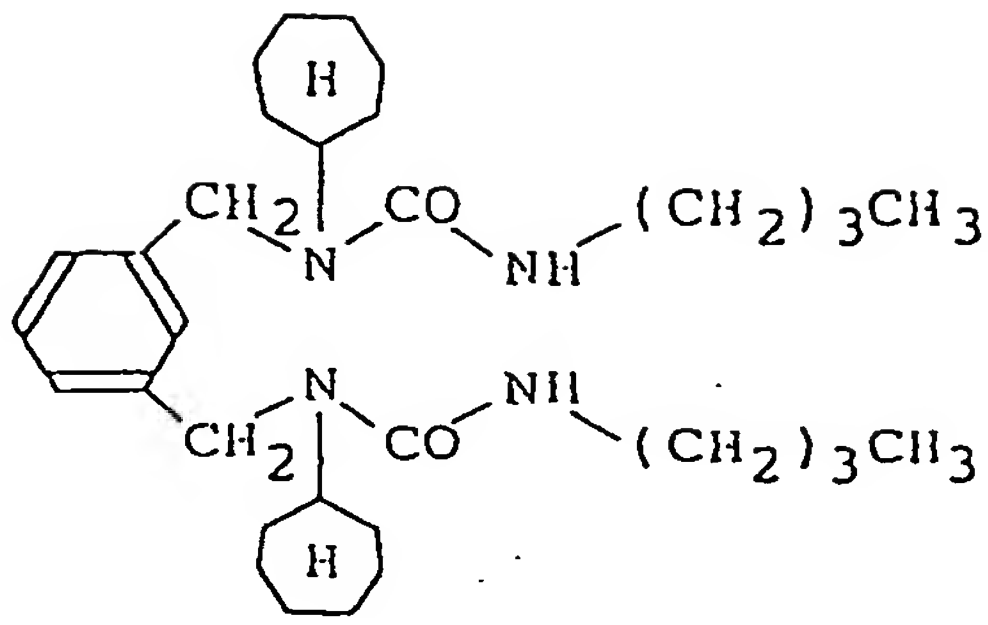


1-[p-(3-t-Butylureidomethyl)benzyl]-3-(2,4-difluoro-phenyl)-1-heptylurea

(i) M.p. 117-119°C
(ii) Mass (EI) m/z 489 ($M^+ + 1$)
(iii) Elemental analysis ($C_{27}H_{38}N_4O_2F_2$)

	C	H	N
Calcd. (%)	66.37	7.84	11.47
Found (%)	66.40	7.81	11.45

Example 4

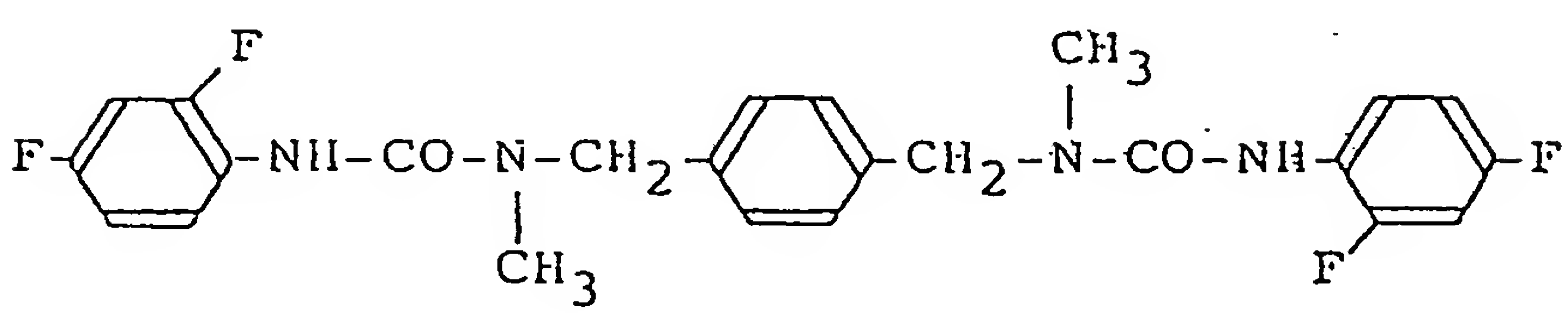


1,3-Bis[(3-butyl-1-cycloheptylyureido)methyl]benzene

(i) M.p. 132-133°C
(ii) Mass (FAB) m/z 527 ($M^+ + 1$)
(iii) Elemental analysis ($C_{32}H_{54}N_4O_2$)

	C	H	N
Calcd. (%)	72.96	10.33	10.64
Found (%)	72.72	10.24	10.44

Example 5

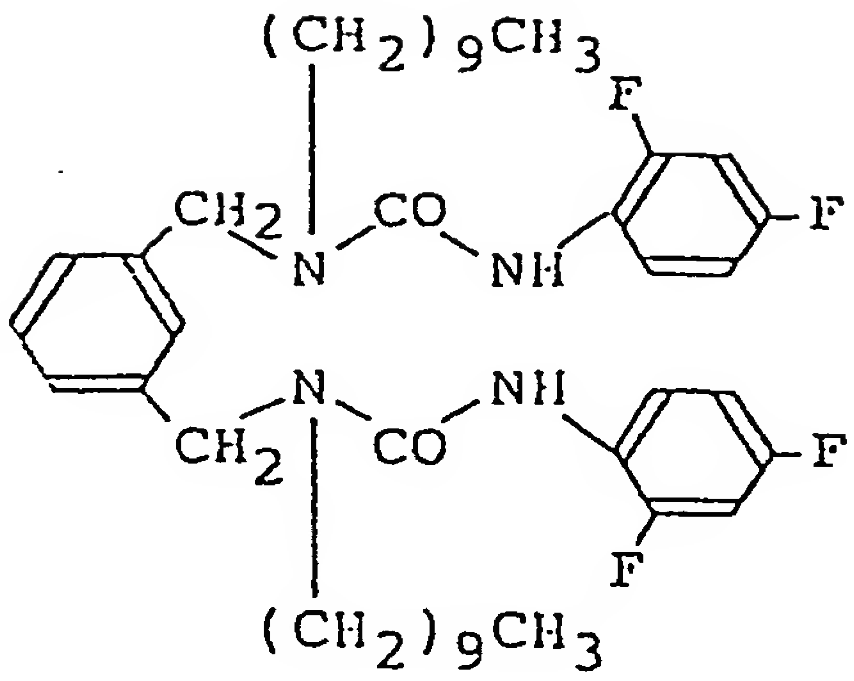


1,4-Bis[[3-(2,4-difluorophenyl)-1-methylureido]-methyl]benzene

(i) M.p. 196-198°C
(ii) Mass (FAB) m/z 475 ($M^+ + 1$)
(iii) Elemental analysis ($C_{24}H_{22}N_4O_2F_4$)

	C	H	N
Calcd. (%)	60.76	4.67	11.81
Found (%)	60.81	4.82	11.61

Example 6



To a solution of 833 mg N,N'-didecyl-m-xylylenediamine in 20 ml n-hexane, was added dropwise with stirring 5 ml of a n-hexane solution containing 620 mg 2,4-difluorophenyl isocyanate under ice cooling. Stirring was continued at room temperature for two hours, the solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography, giving 750 mg of 1,3-bis[[1-decyl-3-(2,4-difluorophenyl)ureido]methyl]benzene.

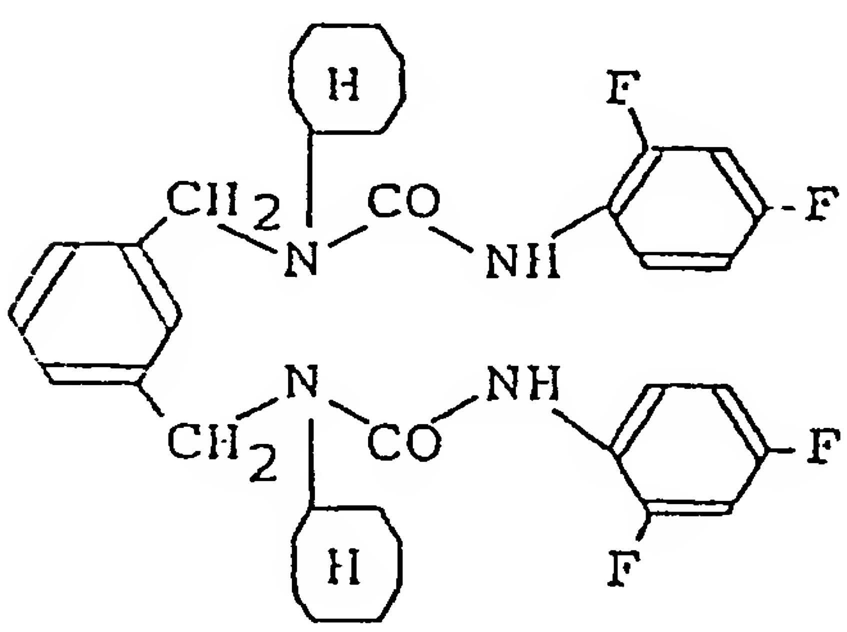
(i) ^{1}H-NMR ($CDCl_3$, δ ppm)

0.88 (6H, t), 3.36 (4H, t), 4.60 (4H, s)

(ii) IR (cm^{-1}), 1660, 1540, 1440

The following seven compounds were prepared in much the same manner as in Example 6.

Example 7



1,3-Bis[[1-cyclooctyl-3-(2,4-difluorophenyl)ureido]-methyl]benzene

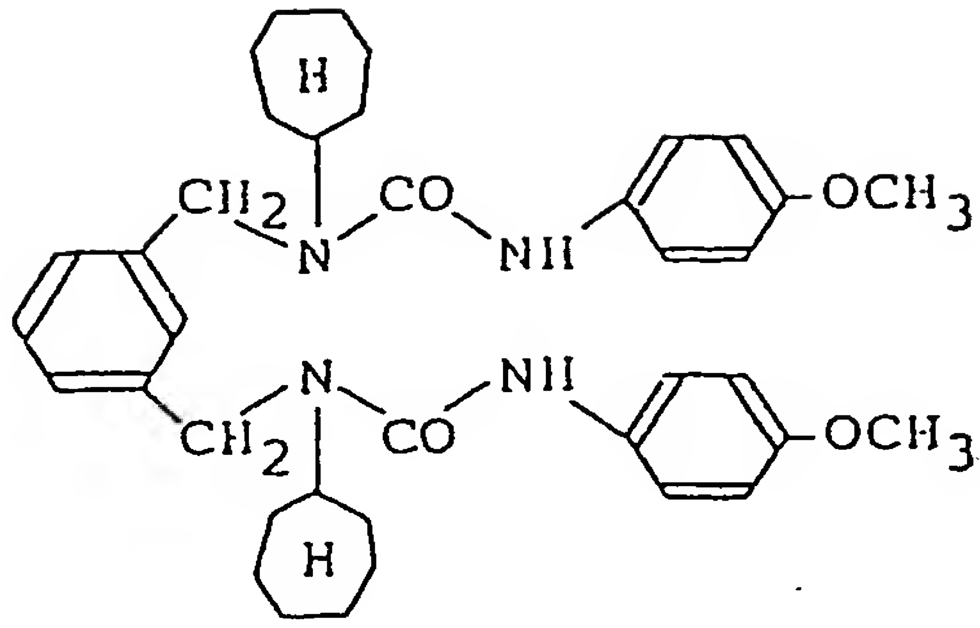
(i) ^{1}H-NMR ($CDCl_3$, δ ppm)

4.48 (4H, s), 6.24 (1H, d), 8.02 (1H, m)

(ii) Mass (FAB) m/z 667 (M^+ + 1)

(iii) IR (cm^{-1}), 1672, 1536, 1432, 1198

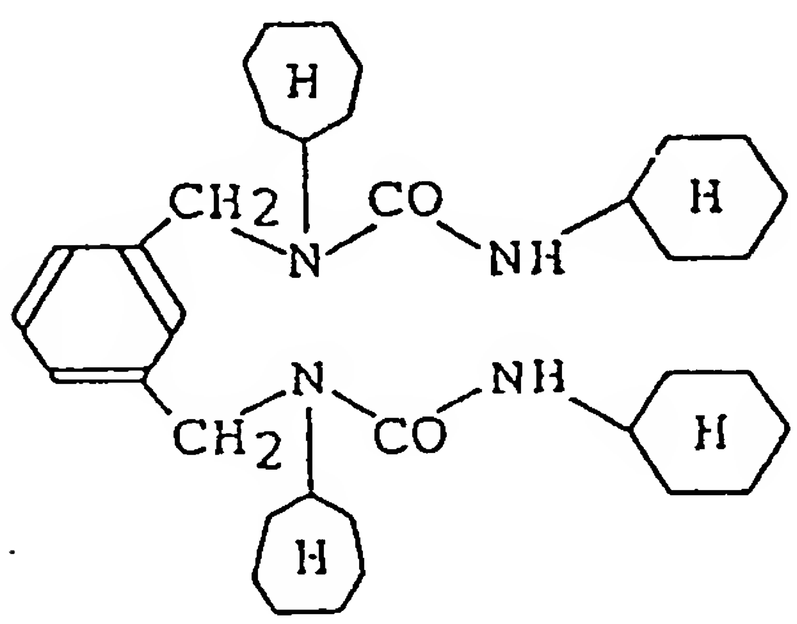
Example 8



1,3-Bis[[1-cycloheptyl-3-(p-methoxyphenyl)ureido]-methyl]benzene

(i) ^{1}H-NMR ($CDCl_3$, δ ppm)
3.74 (6H, s), 4.52 (4H, s), 6.68 (4H, d)
(ii) Mass (FAB) m/z 627 (M^+ + 1)
(iii) IR (cm^{-1}), 1646, 1514, 1232

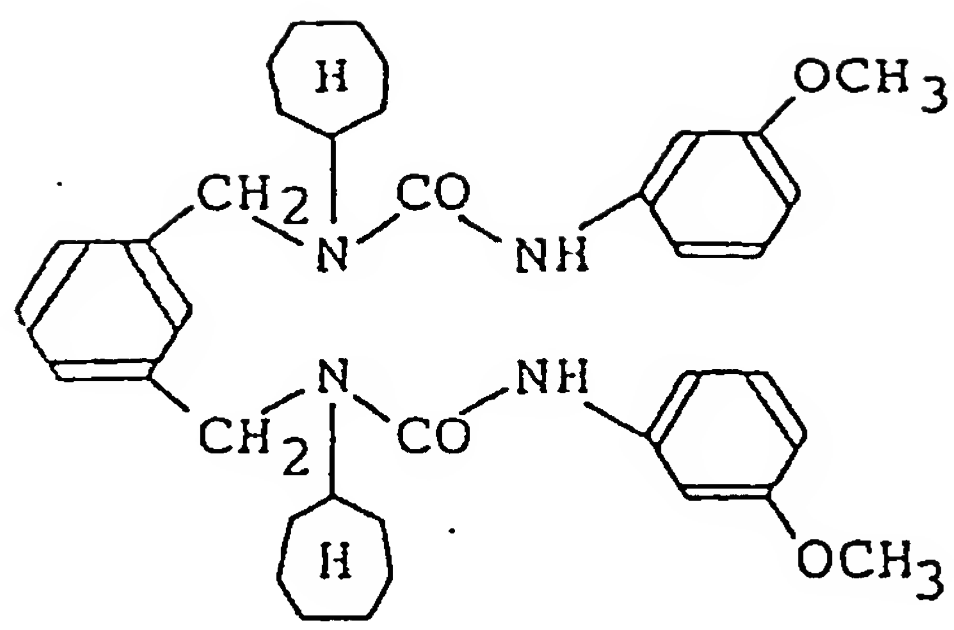
Example 9



1,3-Bis[(1-cycloheptyl-3-cyclohexylureido)methyl]benzene

(i) ^{1}H-NMR ($CDCl_3$, δ ppm)
4.32 (4H, s)
(ii) Mass (FAB) m/z 579 (M^+ + 1)
(iii) IR (cm^{-1}), 2860, 1636, 1530

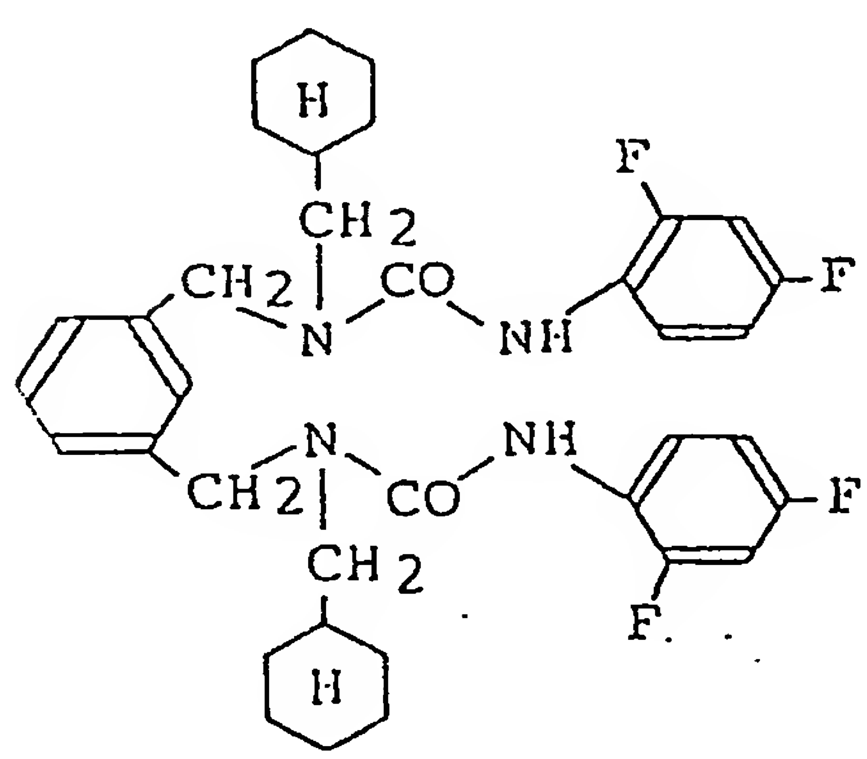
Example 10



1,3-Bis[[1-cycloheptyl-3-(m-methoxyphenyl)ureido]-methyl]benzene

(i) ^{1}H-NMR ($CDCl_3$, δ ppm)
3.76 (6H, s), 4.48 (4H, s)
(ii) Mass (FAB) m/z 627 ($M^+ + 1$)
(iii) IR (cm^{-1}), 1654, 1608, 1540, 1496, 1456

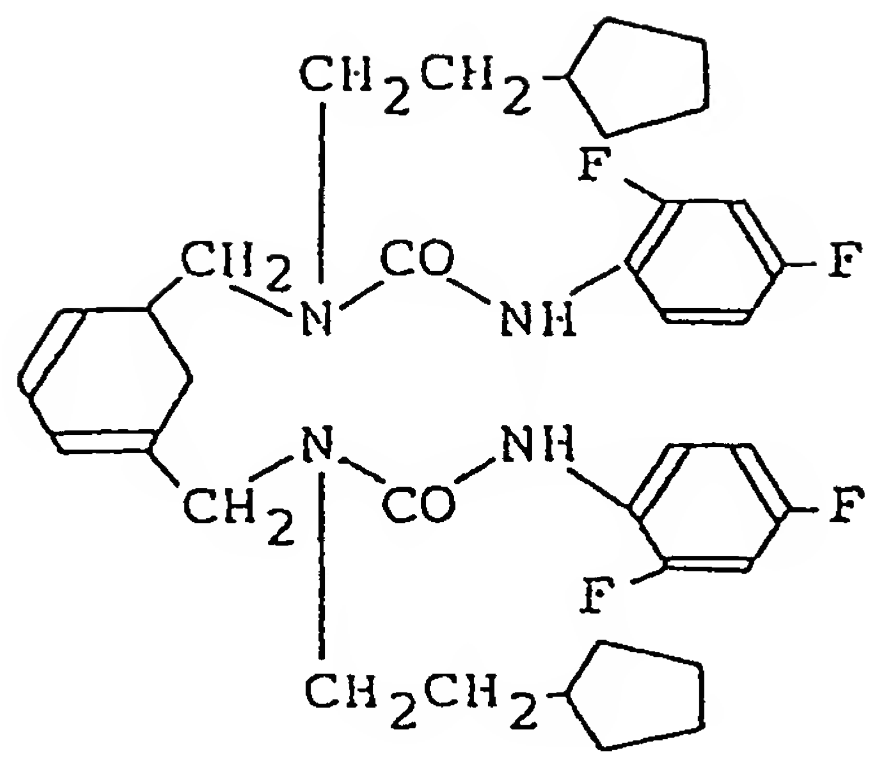
Example 11



1,3-Bis[[3-(2,4-difluorophenyl)-1-cyclohexylmethyl-ureido]methyl]benzene

(i) ^{1}H-NMR ($CDCl_3$, δ ppm)
3.18 (4H, d), 3.58 (4H, s), 6.42 (1H, d)
(ii) Mass (FAB) m/z 639 ($M^+ + 1$)
(iii) IR (cm^{-1}), 2936, 1654, 1616, 1524

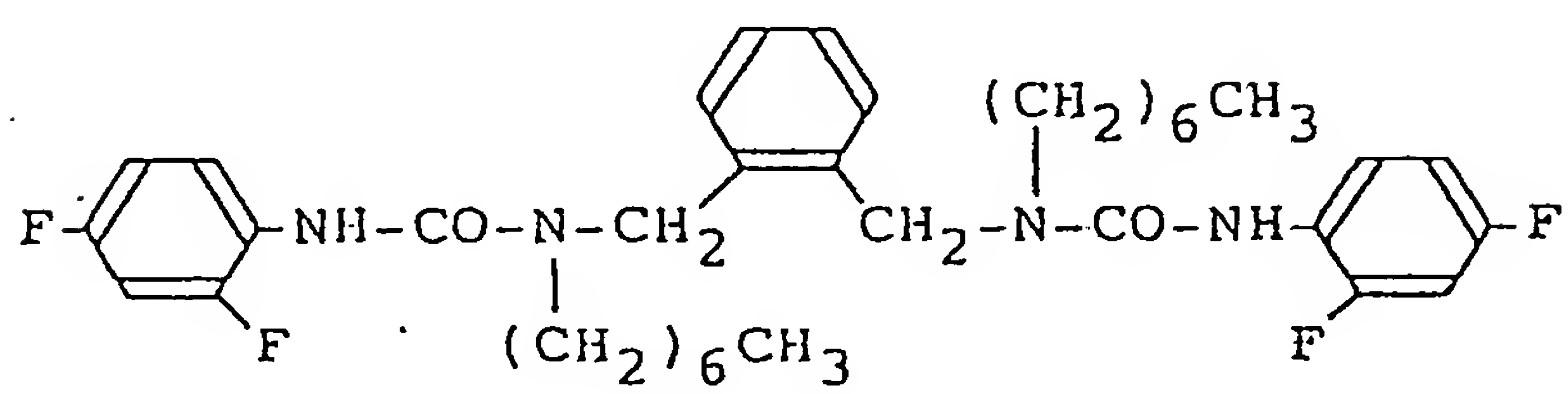
Example 12



1,3-Bis[[3-(2,4-difluorophenyl)-1-cyclopentylethylureido]methyl]benzene

(i) ^{1}H-NMR ($CDCl_3$, δ ppm)
3.36 (4H, t), 4.60 (4H, s), 6.42 (1H, d)
(ii) Mass (FAB) m/z 439 (M^+ - 1)
(iii) IR (cm^{-1}), 2960, 1652, 1616, 1532, 1434

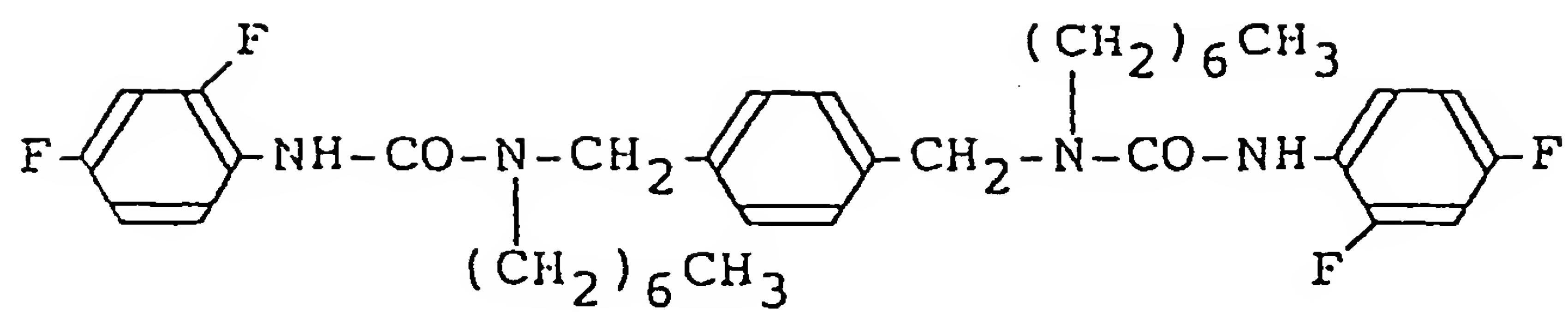
Example 13



1,2-Bis[[3-(2,4-difluorophenyl)-1-heptylureido]-methyl]benzene

(i) ^{1}H-NMR ($CDCl_3$, δ ppm)
0.88 (6H, t), 3.36 (4H, t), 4.68 (4H, s)
(ii) Mass (FAB) m/z 643 (M^+ + 1)

Example 14



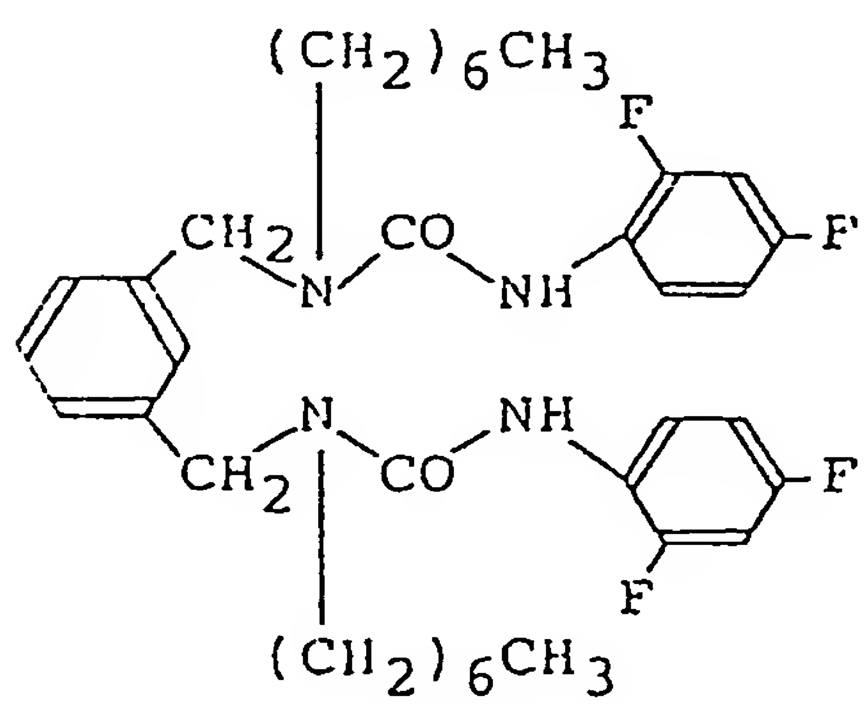
To a solution of 1.5 g N,N'-diheptyl-p-xylylenediamine in 20 ml n-hexane, was added dropwise with stirring 5 ml of a n-hexane solution containing 1.4 g 2,4-difluorophenyl isocyanate under ice cooling. Stirring was continued at room temperature for two hours, and the solid which separated out was collected by filtration and recrystallized from methanol, giving 2.3 g of 1,4-bis[[1-heptyl-3-(2,4-difluorophenyl)ureido]methyl]benzene.

(i) M.p. 107-108°C
(ii) Mass (EI) m/z 642 (M^+)
(iii) Elemental analysis ($C_{36}H_{46}N_4O_2F_4$)

	C	H	N
Calcd. (%)	67.27	7.21	8.72
Found (%)	67.23	7.25	8.71

The following twelve compounds were prepared in much the same manner as in Example 14.

Example 15

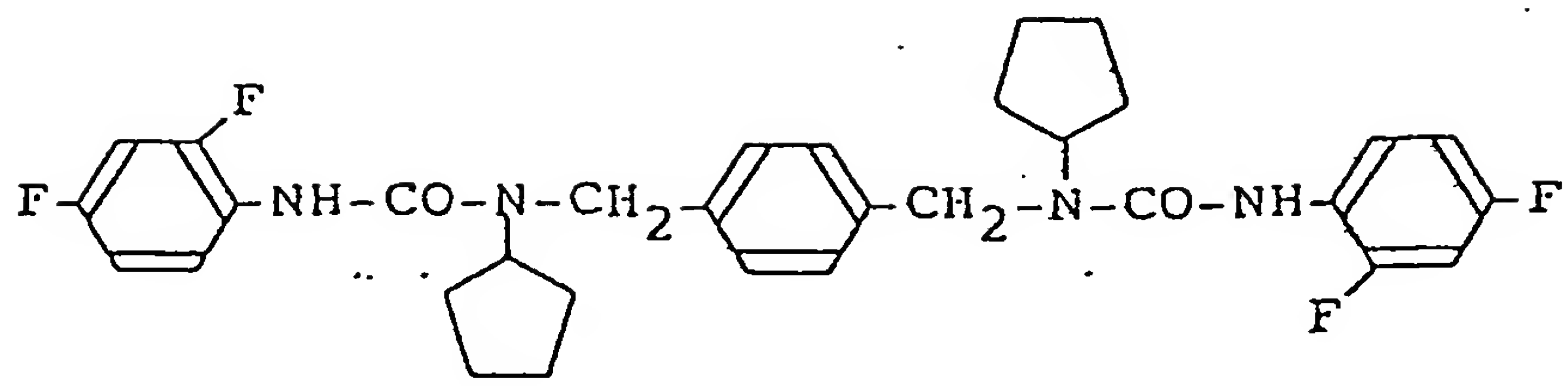


1,3-Bis[[3-(2,4-difluorophenyl]-1-heptylureido]-methyl]benzene

(i) M.p. 69-70°C
(ii) Mass (FAB) m/z 643 ($M^+ + 1$)
(iii) Elemental analysis ($C_{36}H_{46}N_4O_2F_4$)

	C	H	N
Calcd. (%)	67.27	7.21	8.72
Found (%)	67.23	7.33	8.70

Example 16

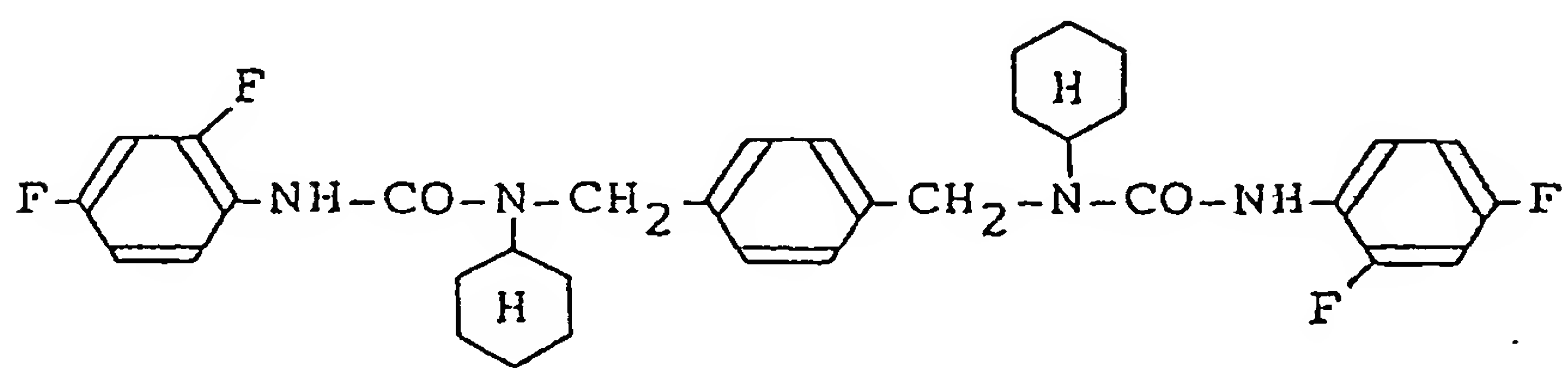


1,4-Bis[[1-cyclopentyl-3-(2,4-difluorophenyl)ureido]-methyl]benzene.

(i) M.p. 165-167°C
(ii) Mass (FAB) m/z 583 (M^+ + 1)
(iii) Elemental analysis ($C_{32}H_{34}N_4O_2F_4$)

	C	H	N
Calcd. (%)	65.97	5.88	9.62
Found (%)	65.96	5.94	9.58

Example 17

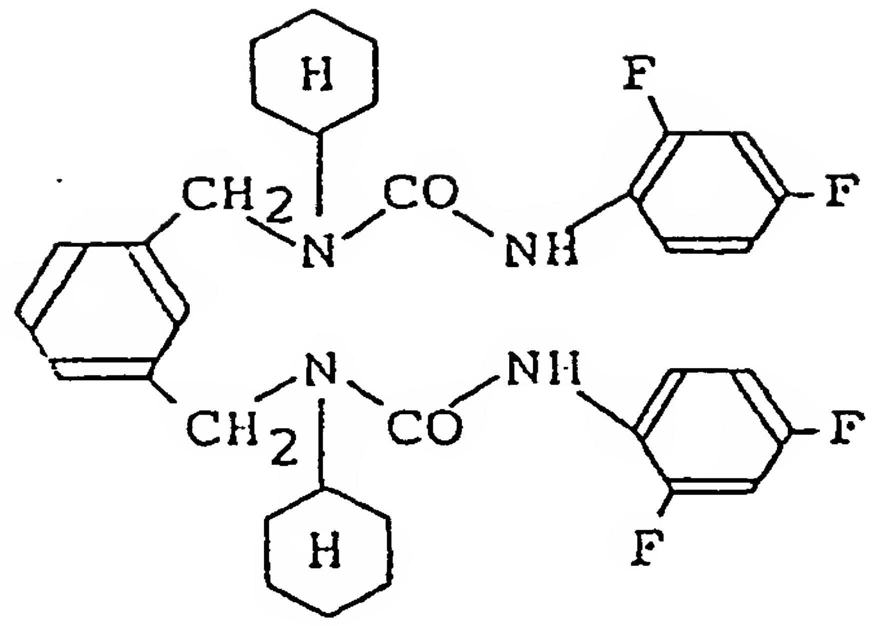


1,4-Bis[[1-cyclohexyl-3-(2,4-difluorophenyl)ureido]-methyl]benzene.

(i) M.p. 176-177°C
(ii) Mass (FAB) m/z 611 (M^+ + 1)
(iii) Elemental analysis ($C_{34}H_{38}N_4O_2F_4$)

	C	H	N
Calcd. (%)	66.87	6.27	9.17
Found (%)	66.69	6.28	9.08

Example 18

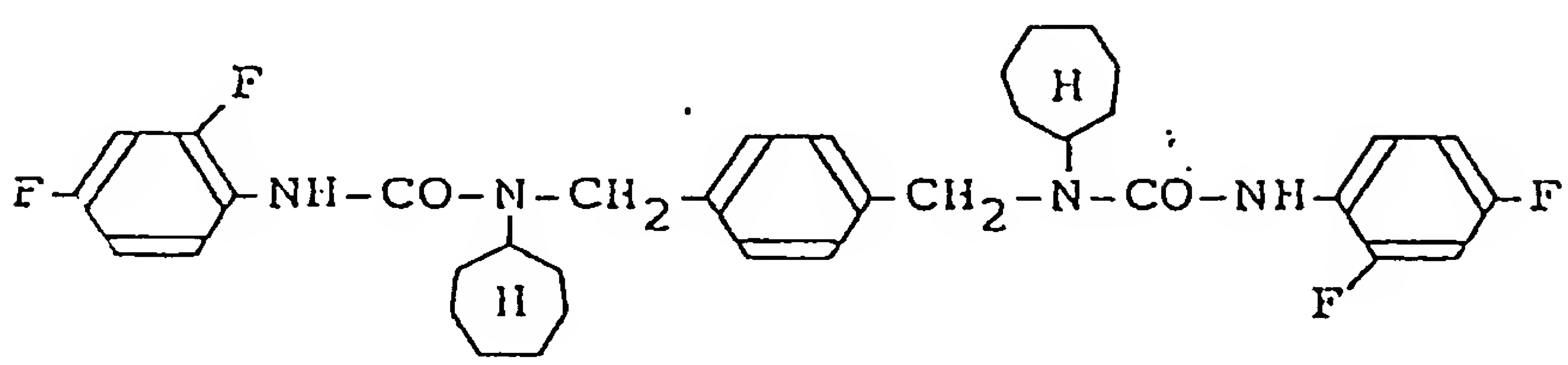


1,3-Bis[[1-cyclohexyl-3-(2,4-difluorophenyl)ureido]-methyl]benzene.

(i) M.p. 98-99°C
(ii) Mass (FAB) m/z 611 ($M^+ + 1$)
(iii) Elemental analysis ($C_{34}H_{38}N_4O_2F_4$)

	C	H	N
Calcd. (%)	66.87	6.27	9.17
Found (%)	66.99	6.21	8.96

Example 19

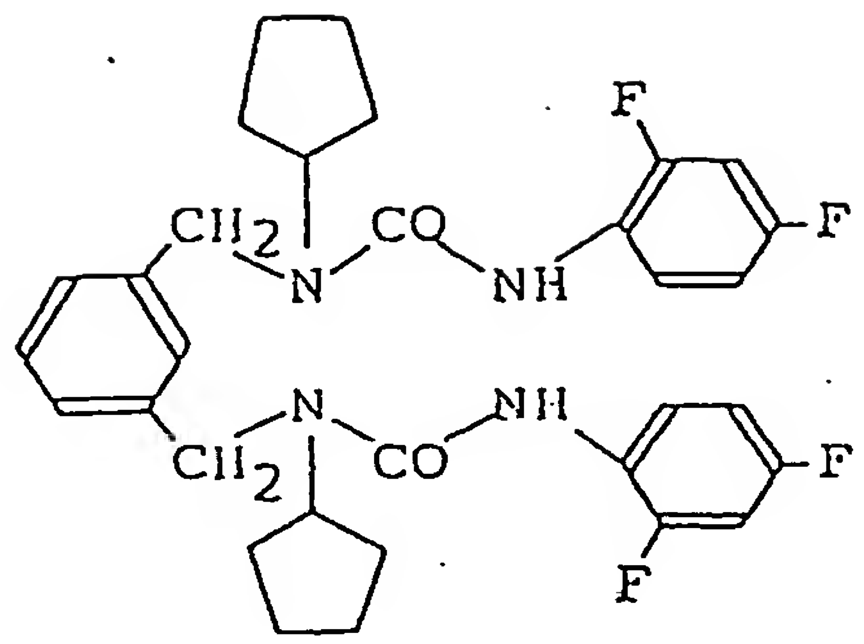


1,4-Bis[[1-cycloheptyl-3-(2,4-difluorophenyl)ureido]-methyl]benzene.

(i) M.p. 89-91°C
(ii) Mass (FAB) m/z 639 ($M^+ + 1$)
(iii) Elemental analysis ($C_{36}H_{42}N_4O_2F_4$)

	C	H	N
Calcd. (%)	67.69	6.63	8.77
Found (%)	67.62	6.81	8.62

Example 20

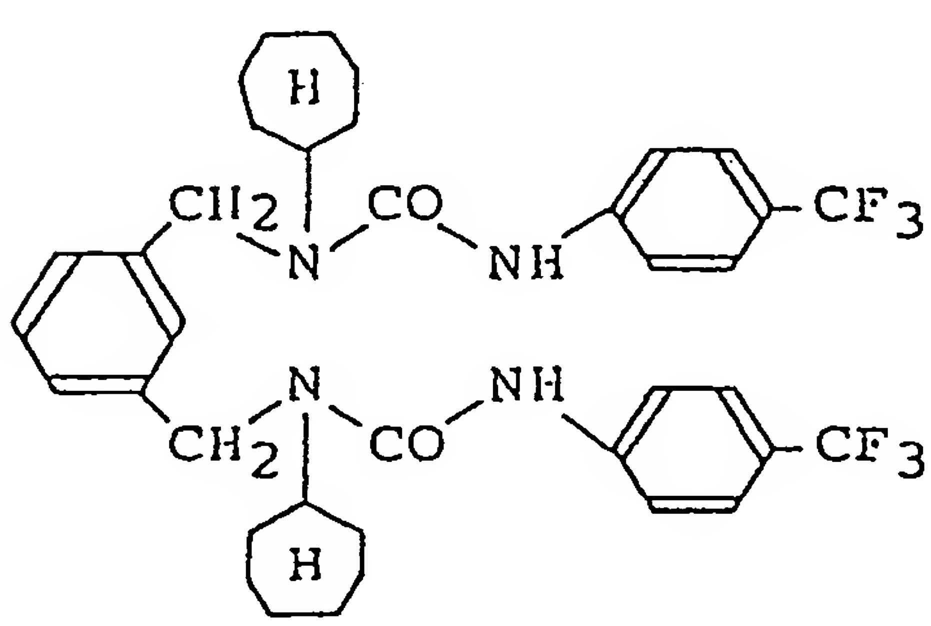


1,3-Bis[[1-cyclopentyl-3-(2,4-difluorophenyl)ureido]-methyl]benzene.

(i) M.p. 150-151°C
(ii) Mass (TAB) m/z 583 (M^+ + 1)
(iii) Elemental analysis ($C_{32}H_{34}N_4O_2F_4$)

	C	H	N
Calcd. (%)	65.97	5.88	9.62
Found (%)	65.73	5.97	9.60

Example 21

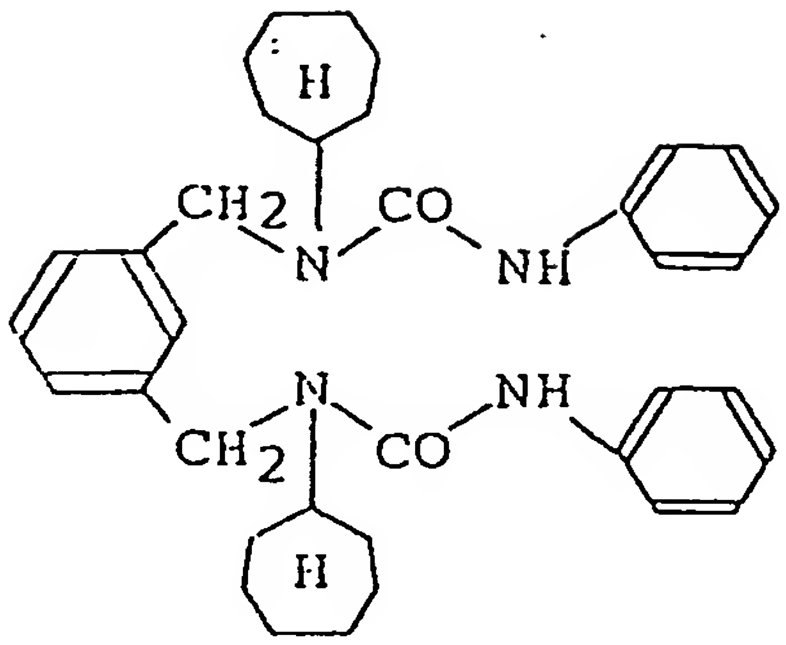


1,3-Bis[[1-cyclopentyl-3-(p-trifluoromethylphenyl)-ureido]methyl]benzene

(i) M.p. 169-170°C
(ii) Mass (FAB) m/z 703 (M^+ + 1)
(iii) Elemental analysis ($C_{38}H_{44}N_4O_2F_6$)

	C	H	N
Calcd. (%)	64.94	6.31	7.97
Found (%)	64.89	6.35	7.94

Example 22

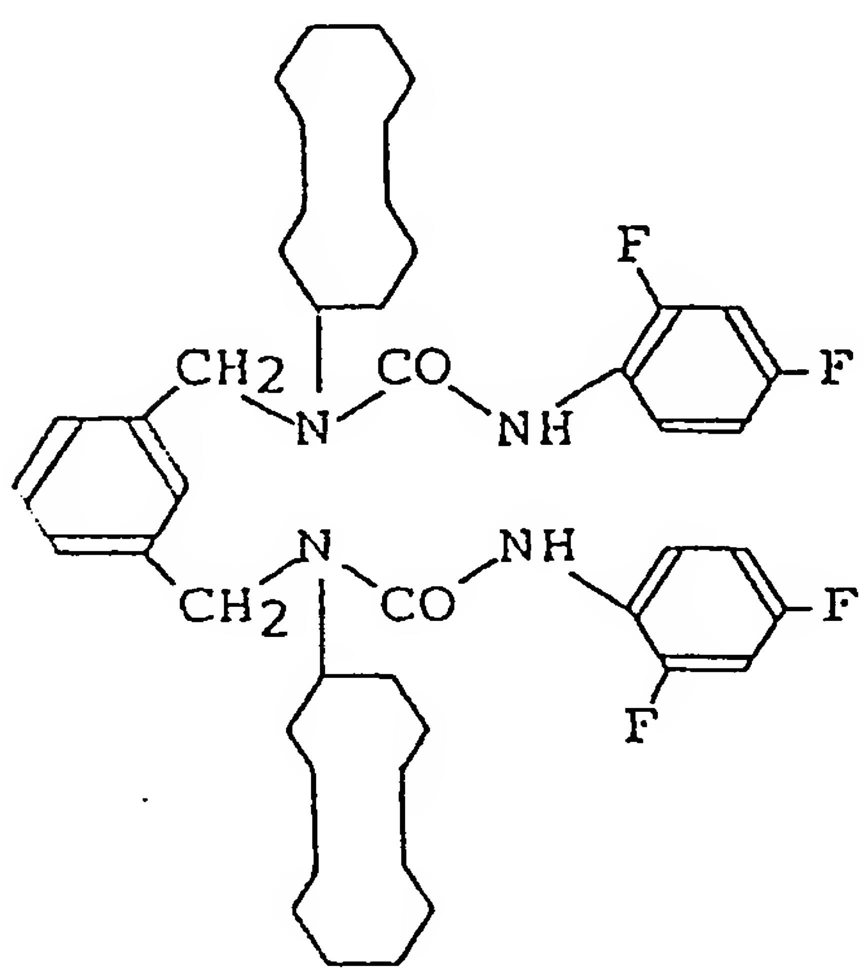


1,3-Bis[(1-cyclohexyl-3-phenylureido)methyl]benzene

(i) M.p. 160-162°C
(ii) Mass (FAB) m/z 567 ($M^+ + 1$)
(iii) Elemental analysis ($C_{36}H_{46}N_4O_2$)

	C	H	N
Calcd. (%)	76.29	8.18	9.88
Found (%)	76.27	8.32	9.83

Example 23

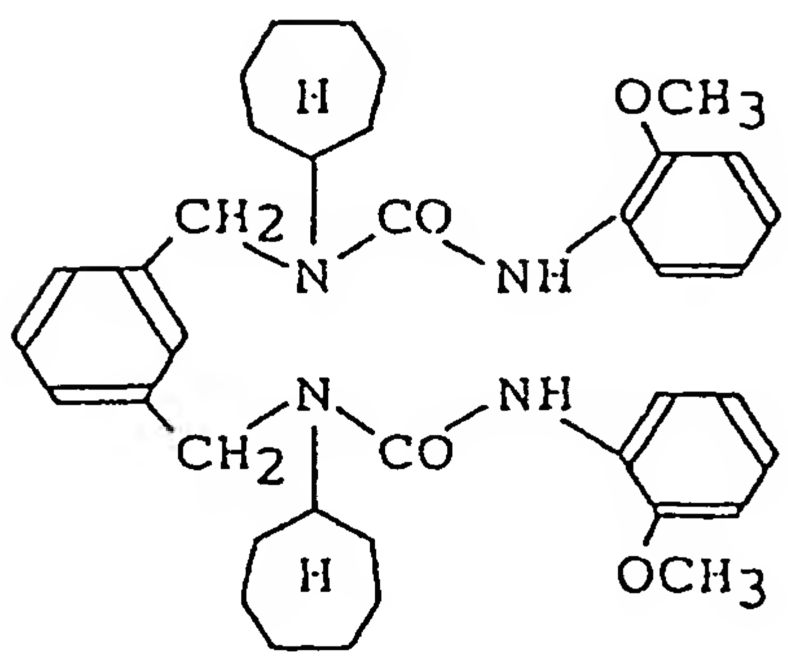


1,3-Bis[[1-cyclododecyl-3-(2,4-difluorophenyl)ureido]-methyl]benzene

(i) M.p. 166-167° C
(ii) Mass (FAB) m/z 779 ($M^+ + 1$)
(iii) Elemental analysis ($C_{46}H_{62}N_4O_2F_4$)

	C	H	N
Calcd. (%)	70.92	8.02	7.19
Found (%)	71.01	8.16	7.05

Example 24

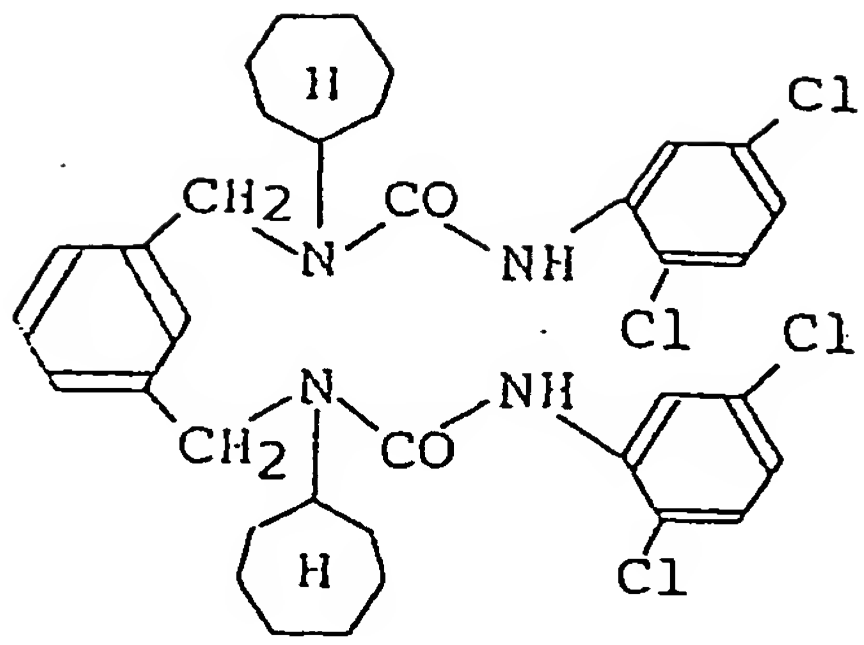


1,3-Bis[[1-cycloheptyl-3-(o-methoxyphenyl)ureido]-methyl]benzene

(i) M.p. 160-162° C
(ii) Mass (FAB) m/z 627 ($M^+ + 1$)
(iii) Elemental analysis ($C_{38}H_{50}N_4O_4$)

	C	H	N
Calcd. (%)	72.81	8.04	8.94
Found (%)	72.78	8.07	8.90

Example 25

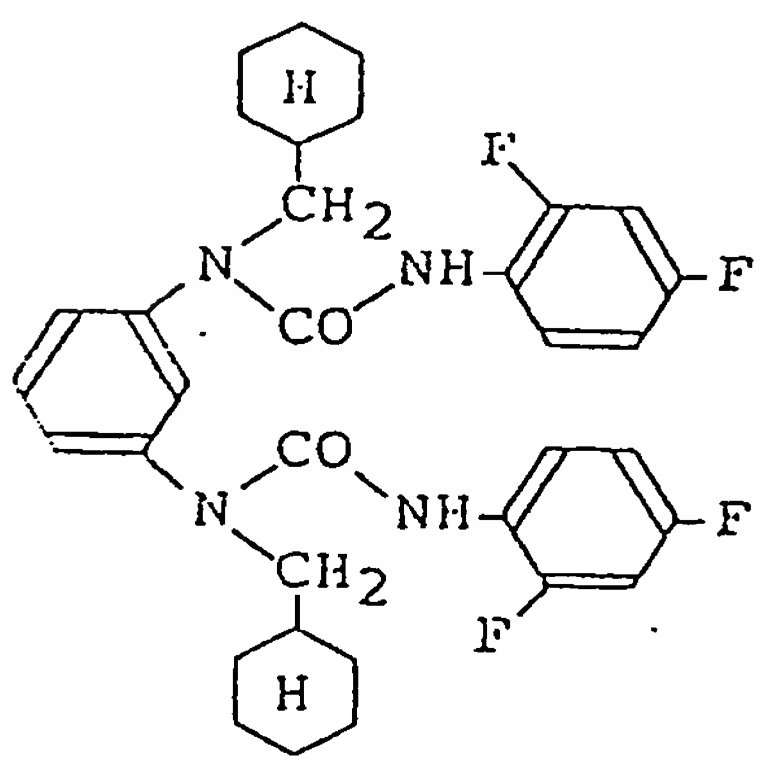


1,3-Bis[[1-cycloheptyl-3-(2,5-dichlorophenyl)ureido]-methyl]benzene

(i) M.p. 153-155°C
(ii) Mass (FAB) m/z 705 ($M^+ + 1$)
(iii) Elemental analysis ($C_{36}H_{42}N_4O_2Cl_4$)

	C	H	N
Calcd. (%)	61.37	6.01	7.95
Found (%)	61.27	5.93	7.93

Example 26

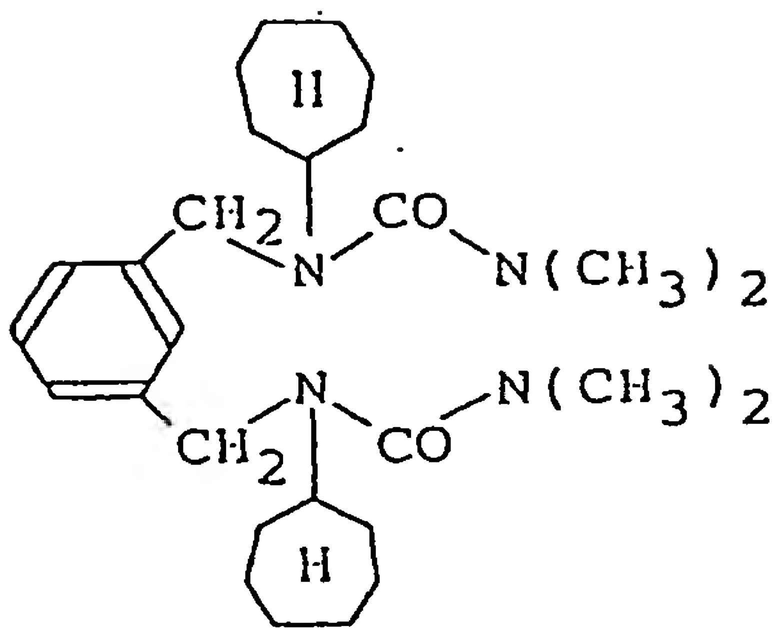


1,3-Bis[1-cyclohexylmethyl-3-(2,4-difluorophenyl)-ureido]benzene

(i) M.p. 183-185°C
(ii) Mass (FAB) m/z 611 ($M^+ + 1$)
(iii) Elemental analysis ($C_{34}H_{38}N_4O_2F_4$)

	C	H	N
Calcd. (%)	66.87	6.27	9.17
Found (%)	66.72	6.40	9.09

Example 27



To a solution of 0.6 g N,N′-dicycloheptyl-m-xylylenediamine and 0.44 g triethylamine in 20 ml methylene dichloride, was added dropwise 5 ml of a methylene dichloride solution containing 0.47 g N,N-dimethylcarbamic chloride, and stirring was continued at room temperature for 12 hours. The reaction mixture was washed with water, dilute hydrochloric acid and water in that order, and dried over a drying agent. After distilling off the solvent, the residue was purified by silica gel column chromatography, giving 0.24 g of 1,3-bis[(1-cycloheptyl-3,3-dimethylureido)methyl]benzene as oil.

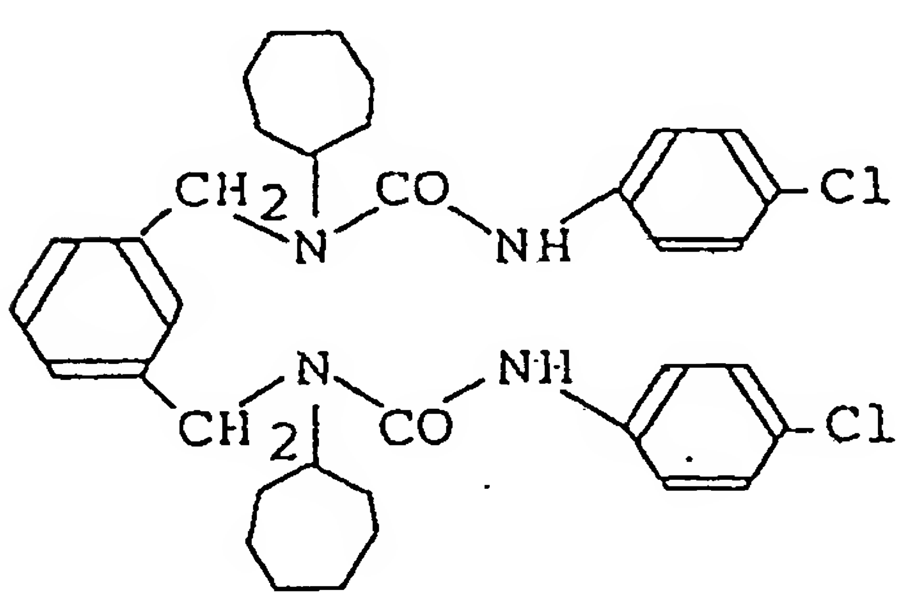
(i) ^{1}H-NMR ($CDCl_3$, δ ppm)

2.80 (12H, s), 4.24 (4H, s)

(ii) Mass (FAB) m/z 471 (M^+ + 1)

(iii) IR (cm^{-1}), 1654, 1492, 1460, 1174

Example 28



To a solution of 0.5 g N,N′-dicycloheptyl-m-xylylenediamine in 50 ml n-hexane, was added dropwise with stirring 5 ml of a n-hexane solution containing 0.25 g 4-chlorophenyl isocyanate under ice cooling, and stirring was continued at room temperature for two hours. After distilling off the solvent under reduced pressure, the residue was purified by silica gel column chromatography, giving 0.9 g of 1,3-bis[[3-(p-chlorophenyl)-1-cycloheptylureido]methyl]benzene as amorphous solid.

(i) ^{1}H-NMR ($CDCl_3$, δ ppm)

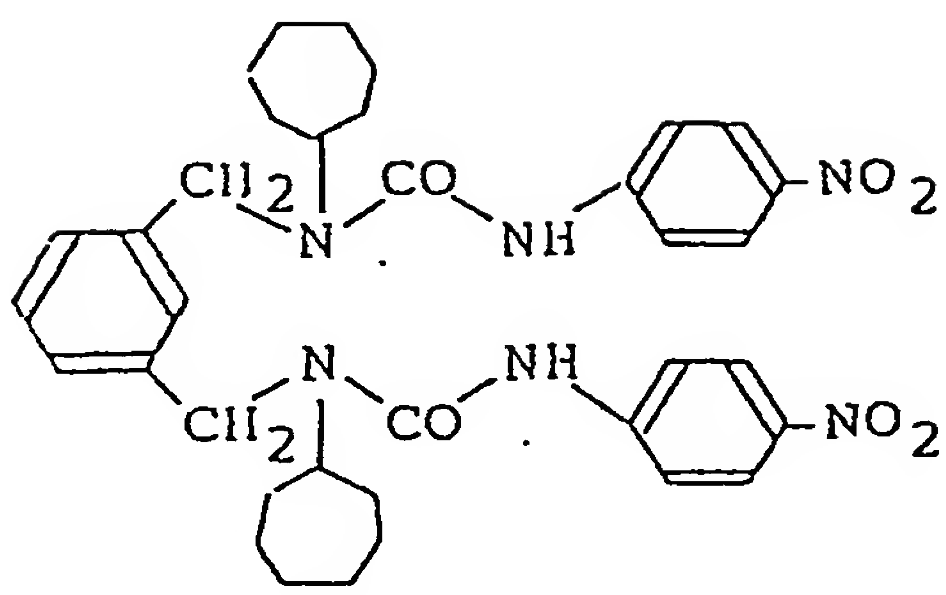
1.20-2.20 (26H, m), 4.48 (4H, s), 1.12 (2H, s)

(ii) Mass (FAB) m/z 635 (M^+)

(iii) IR (cm^{-1}) 1646, 1526, 1496

The following two compounds were perpared in much the same manner as in Example 28.

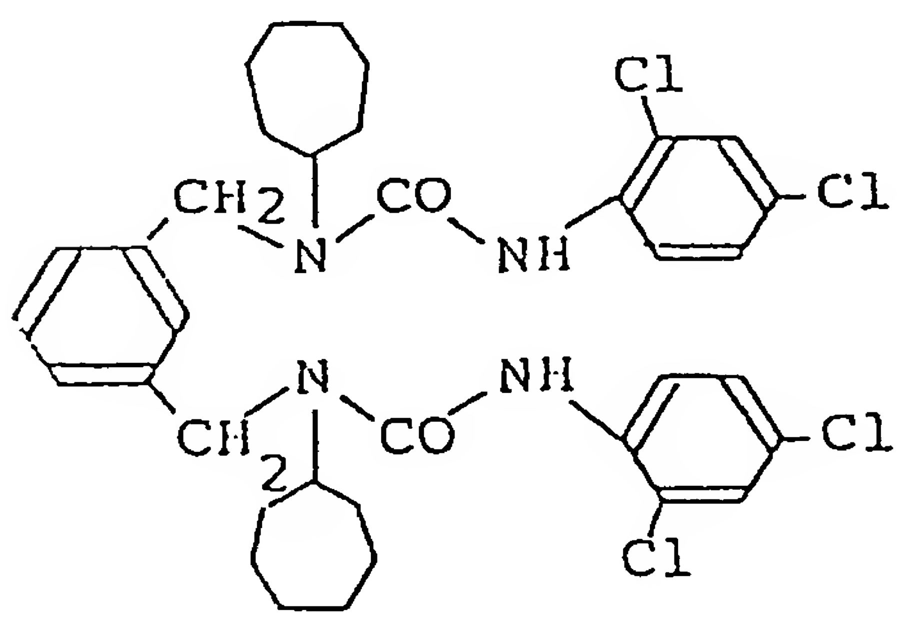
Example 29



1,3-Bis[[1-cycloheptyl-3-(p-nitrophenyl)ureido]-methyl]benzene

(i) ^{1}H-NMR ($CDCl_3$, δ ppm)
4.52 (4H, s), 6.56 (2H, s), 8.04 (4H, d)
(ii) Mass (FAB) m/z 657 (M^+ + 1)
(iii) IR (cm^{-1}), 1674, 1542, 1504, 1334

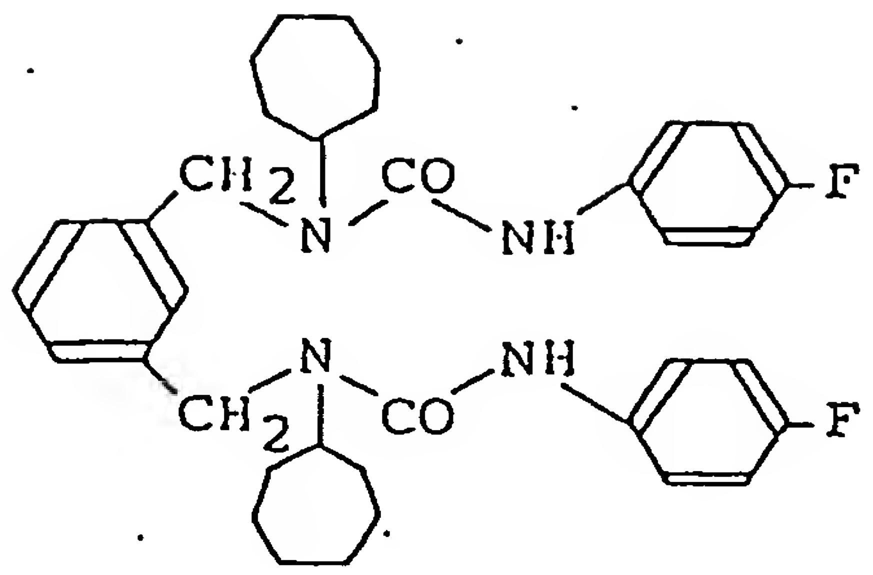
Example 30



1,3-Bis[[1-cycloheptyl-3-(2,4-dichlorophenyl)ureido]-methyl]benzene

(i) ^{1}H-NMR ($CDCl_3$, δ ppm)
4.56 (4H, s), 6.75 (2H, s), 8.18 (2H, d)
(ii) Mass (FAB) m/z 765 (M^+ + 1)
(iii) IR (cm^{-1}), 1678, 1582, 1518, 1302

Example 31



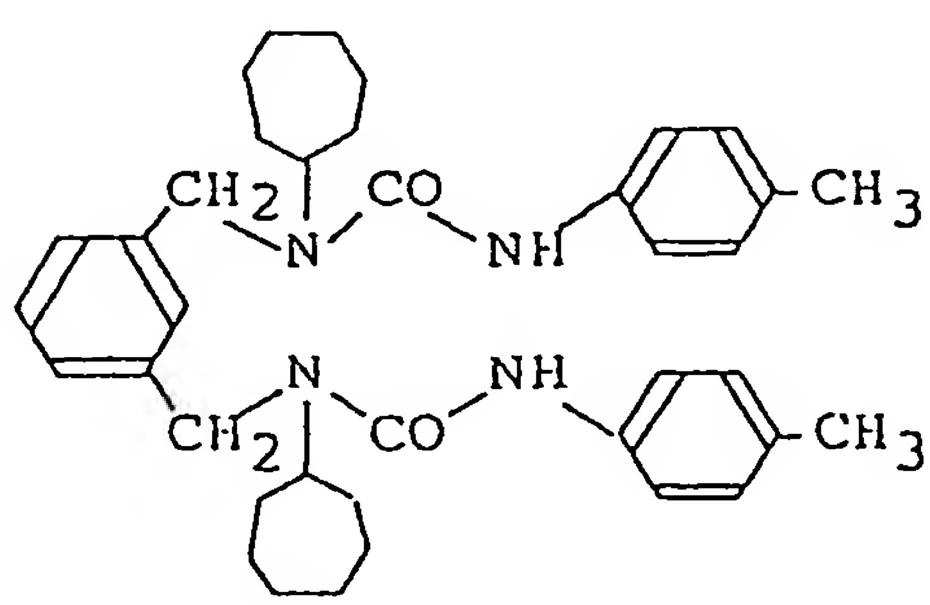
To a solution of 0.5 g N,N'-dicycloheptyl-m-xylylenediamine in 50 ml n-hexane, was added dropwise with stirring 5 ml of a n-hexane solution containing 0.46 g 4-fluorophenyl isocyanate under ice cooling, and stirring was continued at room temperature for two hours. The solid which separated out was collected by filtration, washed with n-hexane and recrystallized from methanol, giving 0.75 g of 1,3-bis[[1-cycloheptyl-3-(p-fluorophenyl)ureido]methyl]benzene.

(i) M.p. 183-185°C
(ii) Mass (FAB) m/z 603 ($M^+ + 1$)
(iii) Elemental analysis ($C_{36}H_{44}N_4O_2F_2$)

	C	H	N
Calcd. (%)	71.74	7.36	9.29
Found (%)	71.70	7.37	9.29

The following seven compounds were prepared in much the same manner as in Example 31.

Example 32

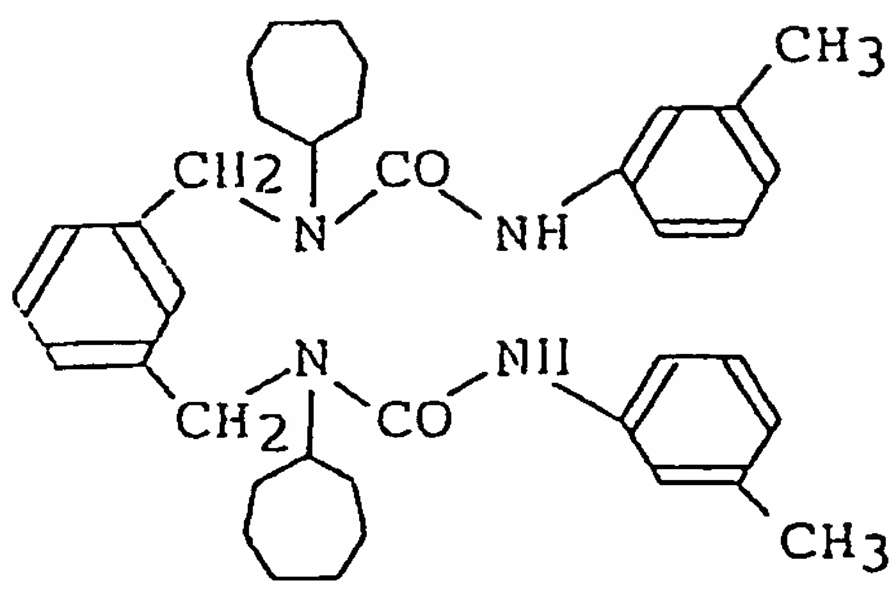


1,3-Bis[[1-cycloheptyl-3-(p-tolyl)ureido]-methyl]benzene

(i) M.p. 147-148°C
(ii) Mass m/z 595 ($M^+ + 1$)
(iii) Elemental analysis ($C_{38}H_{50}N_4O_2$)

	C	H	N
Calcd. (%)	76.73	8.47	9.42
Found (%)	76.65	8.54	9.27

Example 33

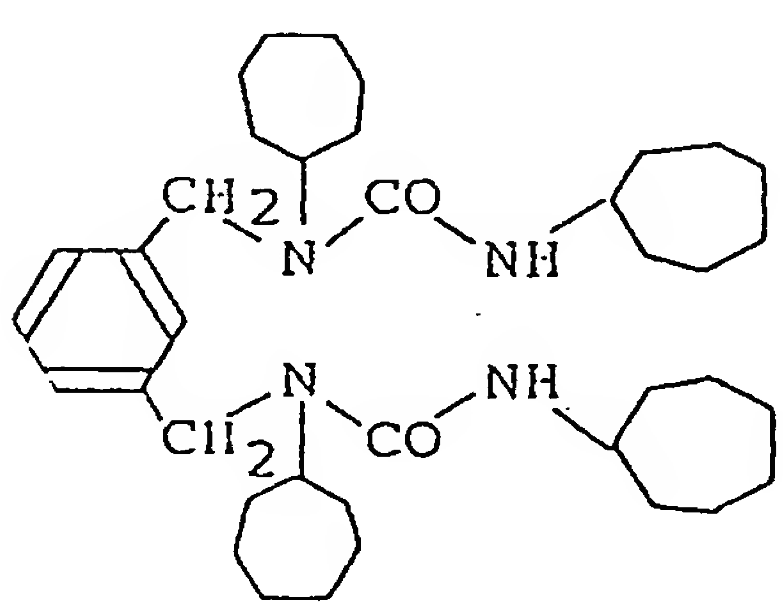


1,3-Bis[[1-cycloheptyl-3-(m-tolyl)ureido]-methyl]benzene

(i) M.p. 171-173°C
(ii) Mass m/z 595 ($M^+ + 1$)
(iii) Elemental analysis ($C_{38}H_{50}N_4O_2$)

	C	H	N
Calcd. (%)	76.73	8.47	9.42
Found (%)	76.65	8.54	9.27

Example 34

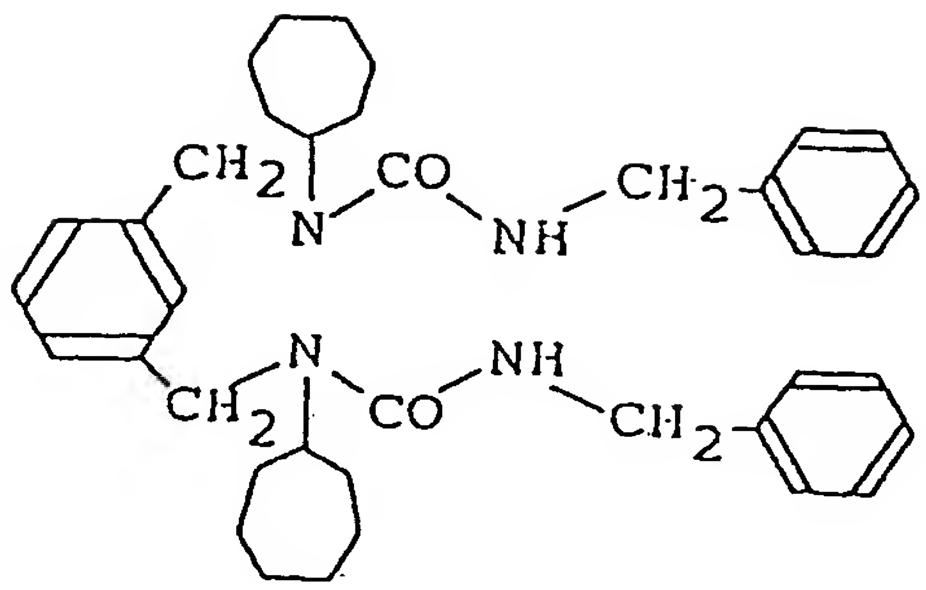


1,3-Bis[(1,3-dicycloheptylureido)methyl]benzene

(i) M.p. 165-167°C
(ii) Mass m/z 607 ($M^+ + 1$)
(iii) Elemental analysis ($C_{38}H_{62}N_4O_2$)

	C	H	N
Calcd. (%)	75.20	10.30	9.23
Found (%)	74.90	10.44	8.95

Example 35

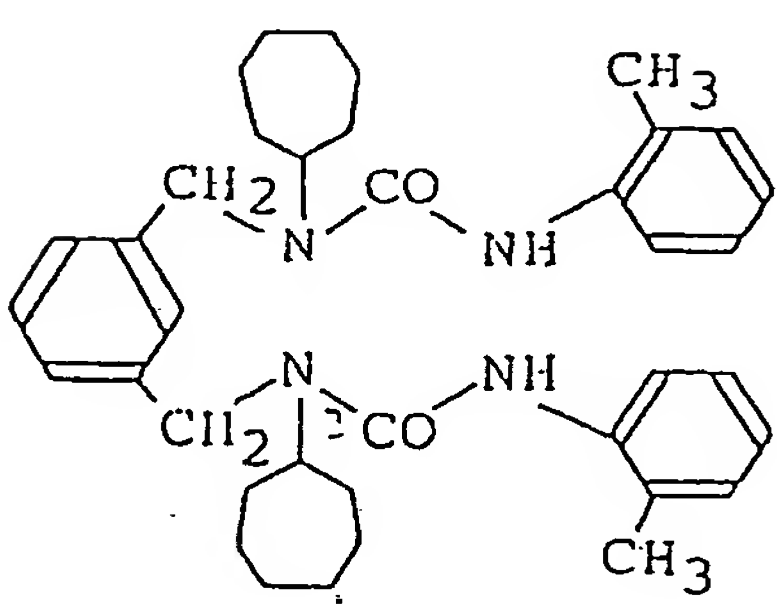


1,3-Bis[(3-benzyl-1-cycloheptylureido)-methyl]benzene

(i) M.p. 173-174° C
(ii) Mass (FAB) m/z 595 (M^+ + 1)
(iii) Elemental analysis ($C_{38}H_{50}N_4O_2$)

	C	H	N
Calcd. (%)	76.73	8.47	9.42
Found (%)	76.74	8.52	9.35

Example 36

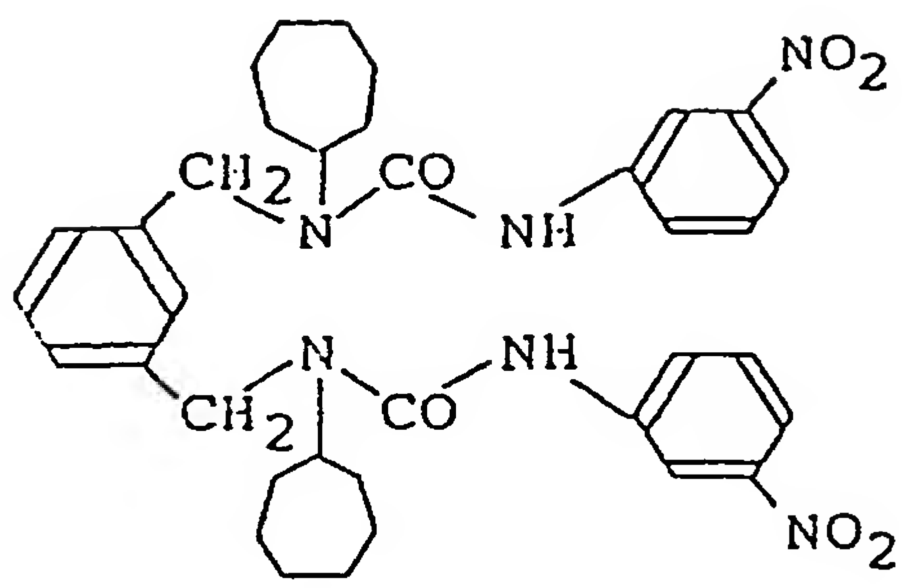


1,3-Bis[[1-cycloheptyl-3-(o-tolyl)ureido]-methyl]benzene

(i) M.p. 183-185° C
(ii) Mass (FAB) m/z 595 (M^+ + 1)
(iii) Elemental analysis

	C	H	N
Calcd. (%)	76.73	8.47	9.42
Found (%)	76.67	8.50	9.33

Example 37

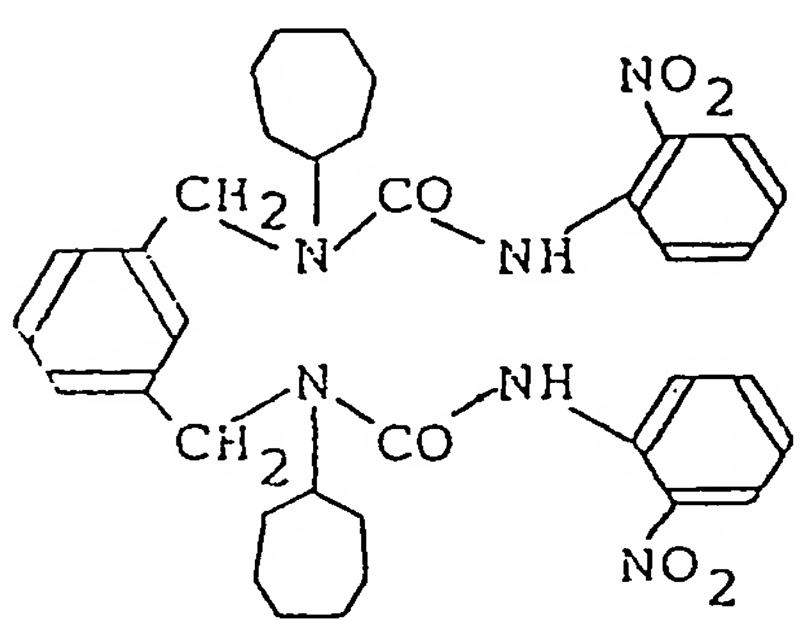


1,3-Bis[[1-cycloheptyl-3-(m-nitrophenyl)ureido]-methyl]benzene

(i) M.p. 200-201°C
(ii) Mass (FAB) m/z 657 ($M^+ + 1$)
(iii) Elemental analysis ($C_{36}H_{44}N_6O_6$)

	C	H	N
Calcd. (%)	65.84	6.75	12.80
Found (%)	65.53	6.68	12.84

Example 38

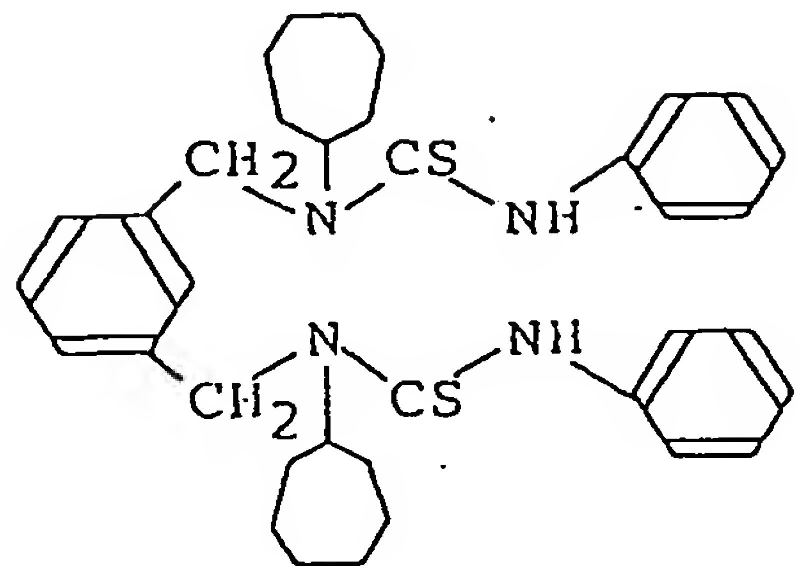


1,3-Bis[[1-cycloheptyl-3-(o-nitrophenyl)ureido]-methyl]benzene

(i) M.p. 144-145°C
(ii) Mass (FAB) m/z 657 ($M^+ + 1$)
(iii) Elemental analysis ($C_{36}H_{44}N_6O_6$)

	C	H	N
Calcd. (%)	65.84	6.75	12.80
Found (%)	65.63	6.71	12.86

Example 39

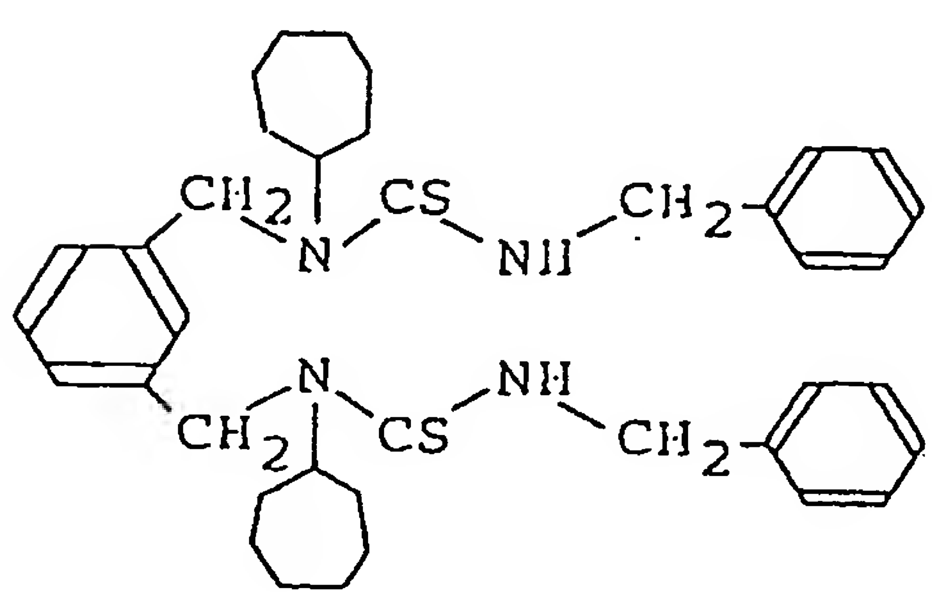


To a solution of 0.5 g N,N'-dicycloheptyl-m-xylylenediamine in 50 ml n-hexane, was added dropwise with stirring 5 ml of a n-hexane solution containing 0.45 g phenyl isothiocyanate under ice cooling, and stirring was continued at room temperature for two hours. The solid which separated out was collected by filtration, and recrystallized from methanol, giving 0.65 g of 1,3-bis[[1-cycloheptyl-3-phenyl(thioureido)]methyl]benzene.

(i) M.p. 146-148°C
(ii) Mass (FAB) m/z 599 ($M^+ + 1$)
(iii) Elemental analysis ($C_{36}H_{46}N_4S_2$)

	C	H	N
Calcd. (%)	72.20	7.74	9.35
Found (%)	72.21	7.84	9.07

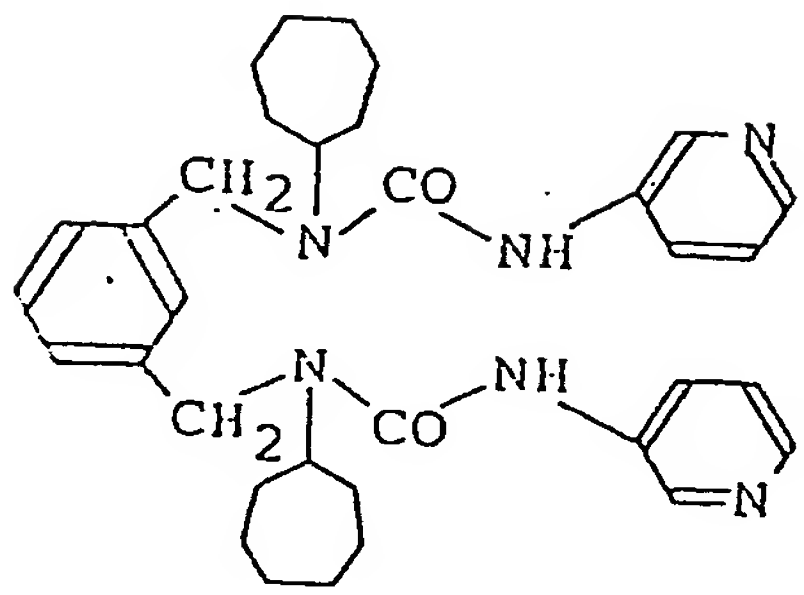
Example 40



To a solution of 0.5 g N,N'-dicycloheptyl-m-xylylenediamine in 50 ml n-hexane, was added dropwise with stirring 5 ml of a n-hexane solution containing 0.5 g benzyl iso-thiocyanate under ice cooling, and stirring was continued at room temperature for 12 hours. After distilling off the solvent under reduced pressure, the residue was purified by silica gel column chromatography, giving 0.78 g of 1,3-bis[3-benzyl-1-cycloheptyl(thioureido)methyl]benzene as amorphous solid.

(i) ^1H-NMR ($CDCl_3$, δ ppm)
4.56 (4H, s), 4.74 (4H, d)
(ii) Mass (FAB) m/z 627 ($M^+ + 1$)
(iii) IR (cm^{-1}), 1526, 1380, 1324

Example 41



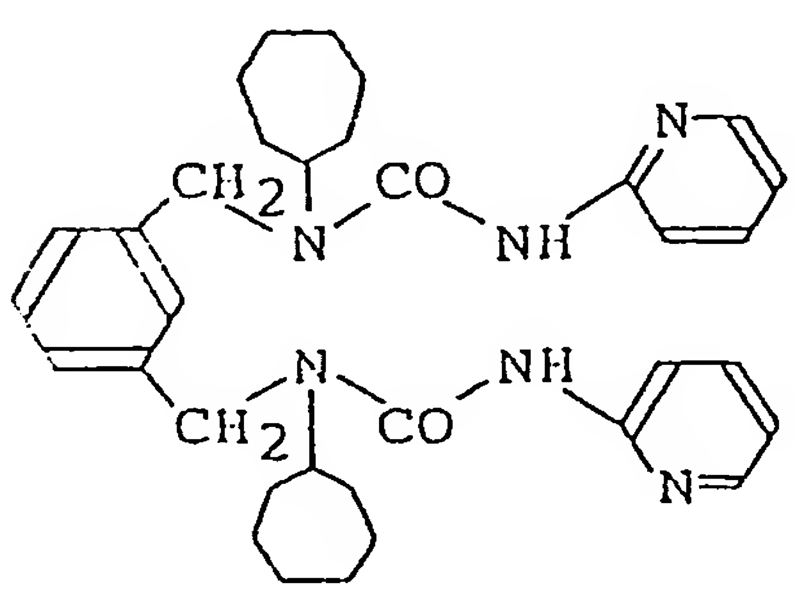
To a solution of 0.5 g N,N'-dicycloheptyl-m-xyxlylenediamine in 30 ml anhydrous toluene, was added 0.5 g β-pyridinecarboxylic azide, and the mixture was heated under reflux for one hour. After confirming cessation of gas evolution, the solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography and then recrystallized from diethyl ether, giving 0.5 g of 1,3-bis[[1-cycloheptyl-3-(3-pyridyl)ureido]methyl]benzene.

(i) M.p. 125-127°C
(ii) Mass (FAB) m/z 569 ($M^+ + 1$)
(iii) Elemental analysis ($C_{34}H_{44}N_6O_2$)

	C	H	N
Calcd. (%)	71.80	7.80	14.78
Found (%)	71.97	7.76	14.65

The following three compounds were prepared in much the same manner as in Example 41.

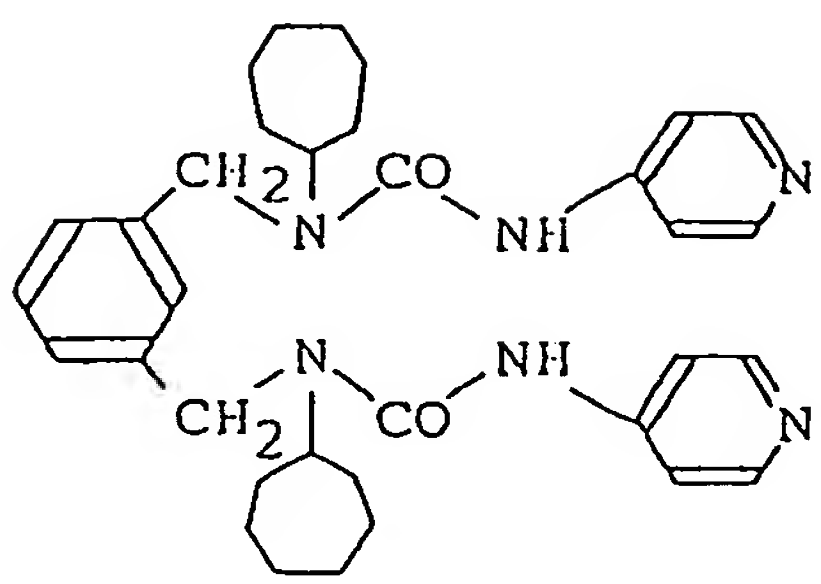
Example 42



1,3-Bis[[1-cycloheptyl-3-(2-pyridyl)ureido]-methyl]benzene

(i) ^{1}H-NMR ($CDCl_3$, δ ppm)
4.55 (4H, s), 7.56 (2H, dd), 7.65 (2H, dd)
(ii) Mass (FAB) m/z 569 ($M^+ + 1$)
(iii) IR (cm^{-1}), 1670, 1518, 1434, 1302

Example 43

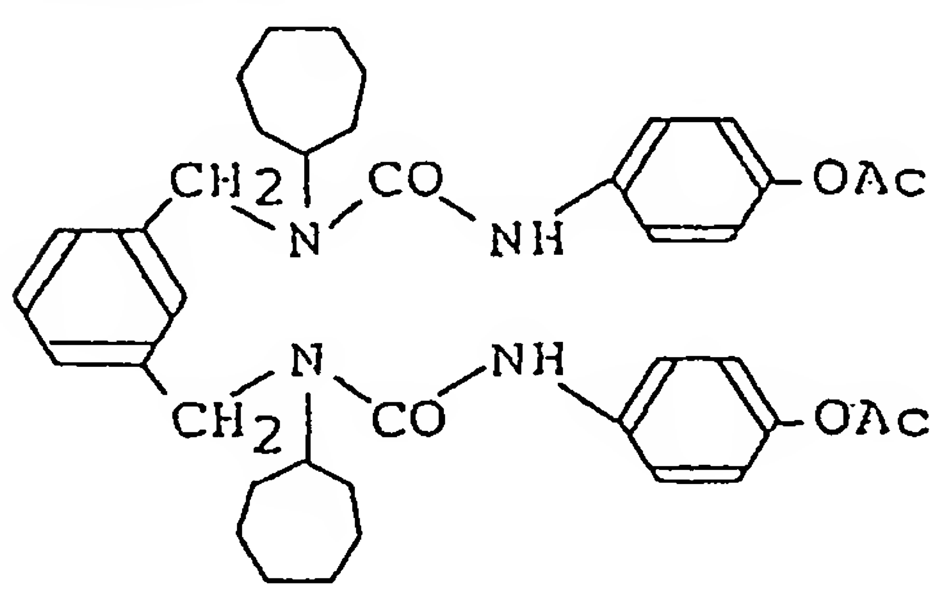


1,3-Bis[[1-cycloheptyl-3-(4-pyridyl)ureido]-methyl]benzene.

(i) M.p. 119-121°C
(ii) Mass (FAB) m/z 569 ($M^+ + 1$)
(iii) Elemental analysis ($C_{34}H_{44}N_6O_2$)

	C	H	N
Calcd. (%)	71.80	7.80	14.78
Found (%)	71.68	7.77	14.87

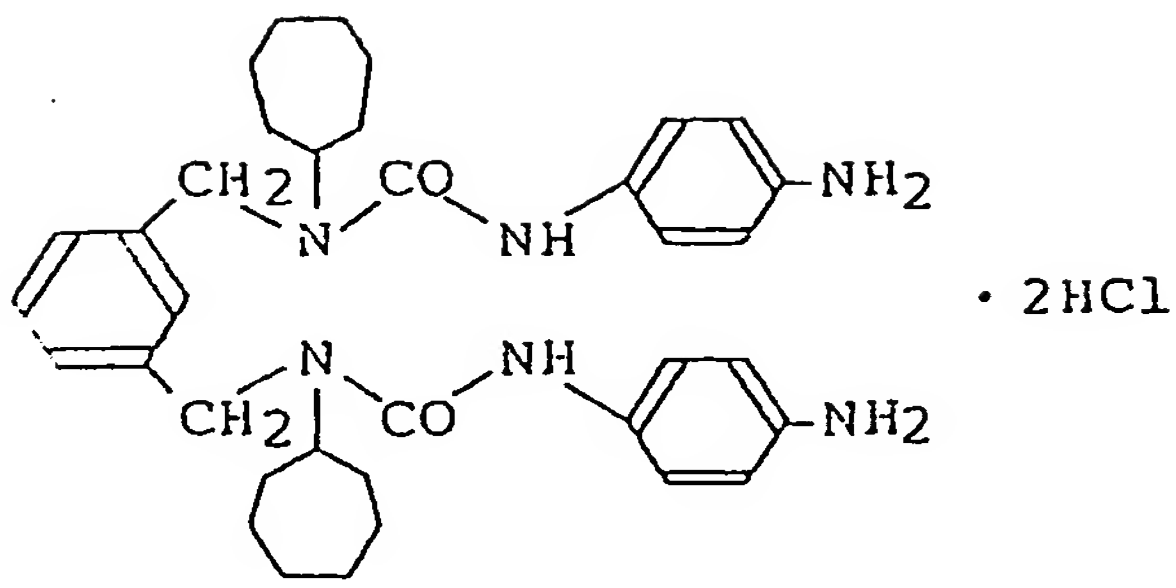
Example 44



1,3-Bis[[3-(p-acetoxyphenyl)-1-cycloheptylureido]-methyl]benzene

1,3-Bis[[3-(p-acetoxyphenyl)-1-cycloheptylureido]methyl]benzene
(i) ^{1}H-NMR ($CDCl_3$, δ ppm)
2.28 (6H, s), 4.50 (4H, s), 6.90 (4H, dd)
(ii) Mass (FAB) m/z 683 ($M^+ + 1$)
(iii) IR (cm^{-1}), 1766, 1652, 1532, 1510

Example 45



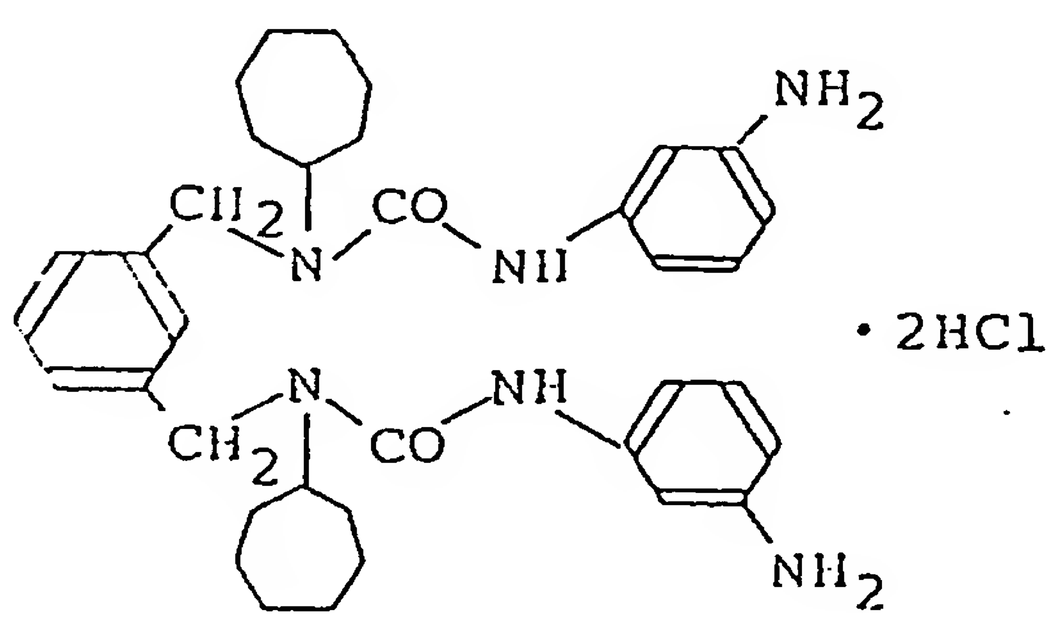
To a solution of 3 g 1,3-bis[[1-cycloheptyl-3-(p-nitrophenyl)ureido]methyl]benzene (compound of Example 30) in 50 ml N,N'-dimethylformamide, was added 300 ml of 10% Pd-carbon powder, and the mixture was subjected to catalytic hydrogenation. After a predetermined volume of hydrogen gas was absorbed, the catalyst was filtered off, the solvent was distilled off under reduced pressure from the filtrate, and the residue was purified by silica gel column chromatography, giving 1.5 g of 1,3-bis[[3-(p-aminophenyl)-1-cycloheptylureido]methyl]benzene as amorphous powder. This was treated with ethanolic hydrogen chloride, and the solid thus obtained was recrystallized from aqueous ethanol, afforiding 1.1 g of 1,3-bis[[1-cycloheptyl-3-(p-aminophenyl)ureido]methyl]benzene dihydrochloride.

(i) M.p. 228-232° C (dec.)
(ii) Mass (FAB) m/z 597 ($M^+ + 1$)
(iii) Elemental analysis ($C_{36}H_{50}N_6O_2Cl_2$)

	C	H	N
Calcd. (%)	64.56	7.52	12.55
Found (%)	64.28	7.53	12.48

The following two compounds were prepared in much the same manner as in Example 45.

Example 46

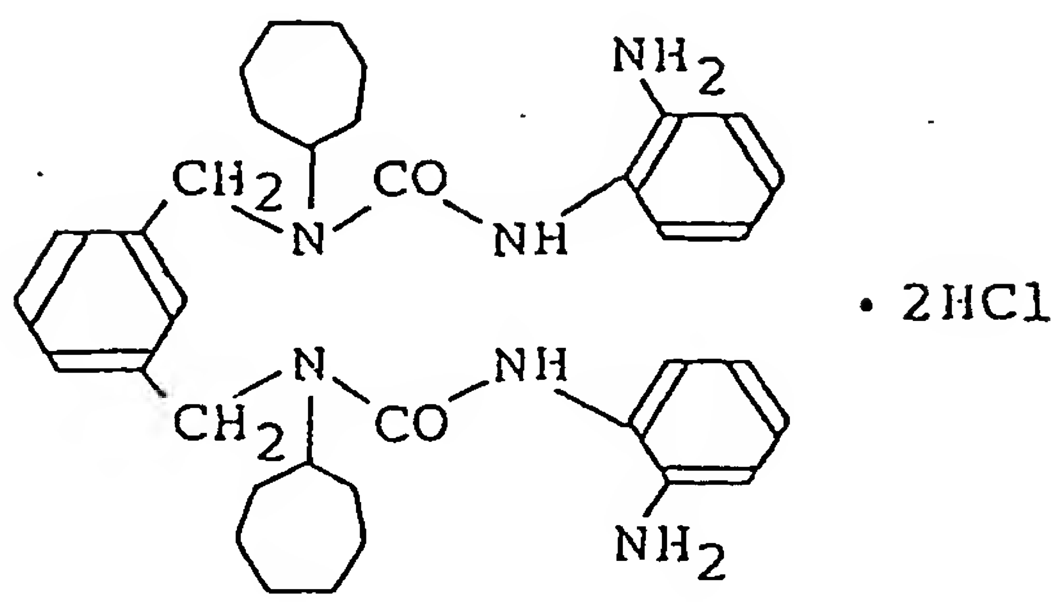


1,3-Bis[[3-(m-aminophenyl)-1-cycloheptylureido]-methyl]benzene dihydrochloride

(i) ^{1}H-NMR (DMSO-d_6, δ ppm)
4.56 (4H, s), 8.60 (2H, s)
(ii) Mass (FAB) m/z 597 ($M^+ + 1$)

(iii) IR (cm^{-1}), 1642, 1610, 1542, 1496

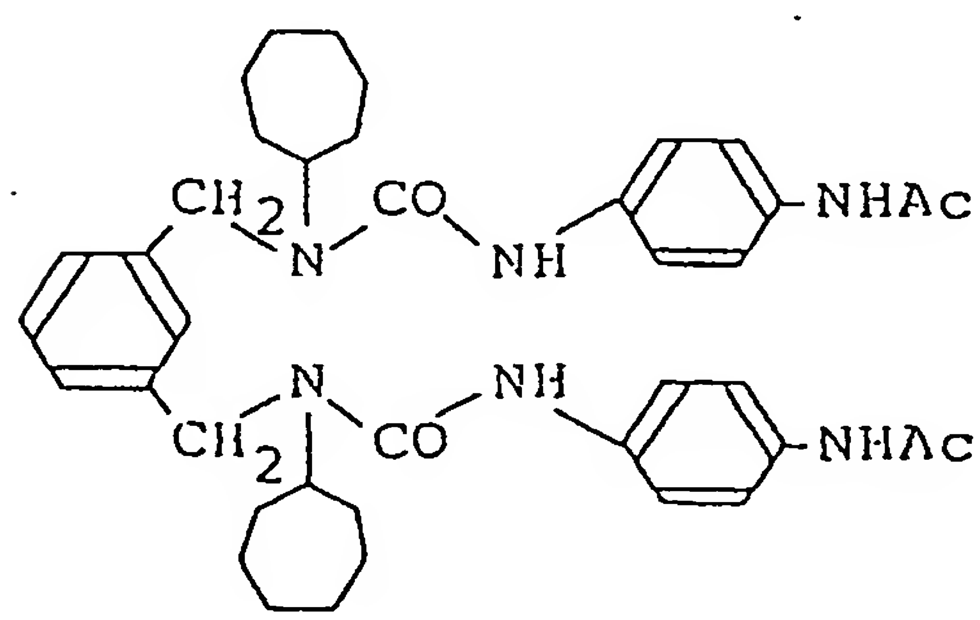
Example 47



1,3-Bis[[3-(o-aminophenyl)-1-cycloheptylureido]-methyl]benzene dihydrochloride

(i) ^{1}H-NMR (DMSO-d_6, δ ppm)
4.56 (4H, s), 8.65 (2H, s)
(ii) Mass (FAB) m/z 597 (M^+ + 1)
(iii) IR (cm^{-1}), 1636, 1522, 1458

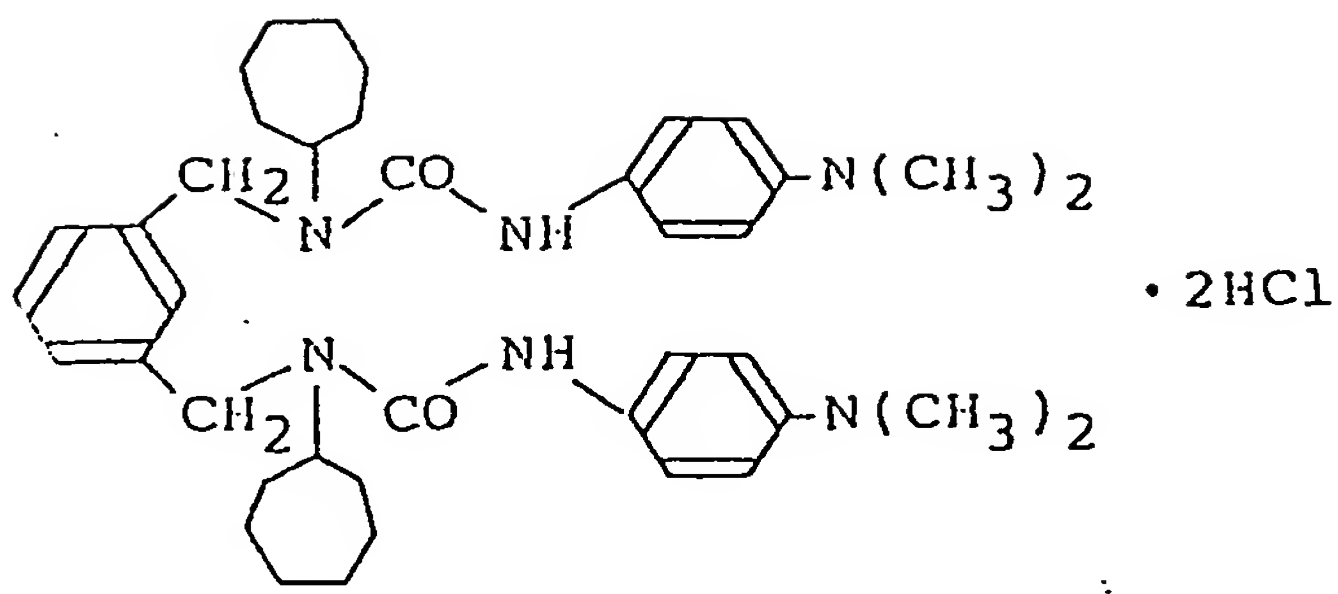
Example 48



To a solution of 0.29 g 1,3-bis[[3-(p-aminophenyl)-1-cycloheptylureido]methyl]benzene (compound of Example 45) and 0.12 g triethylamine in 30 ml dichloromethane, was added dropwise with stirring 5 ml of a dichloromethane solution containing 92 mg acetyl chloride under ice cooling, and stirring was continued at room temperature for two hours. The reaction mixture was washed with dilute hydrochloric acid and water in that order, the solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography, giving 150 mg of 1,3-bis[[3-(p-acetamidophenyl)-1-cycloheptylureido]methyl]benzene as amorphous solid.

(i) ^{1}H-NMR ($CDCl_3$, δ ppm)
2.10 (6H, s), 4.08 (4H, s), 7.00 (4H, d)
(ii) Mass (FAB) m/z 681 (M^+ + 1).
(iii) IR (cm^{-1}), 1666, 1650, 1614, 1556

Example 49

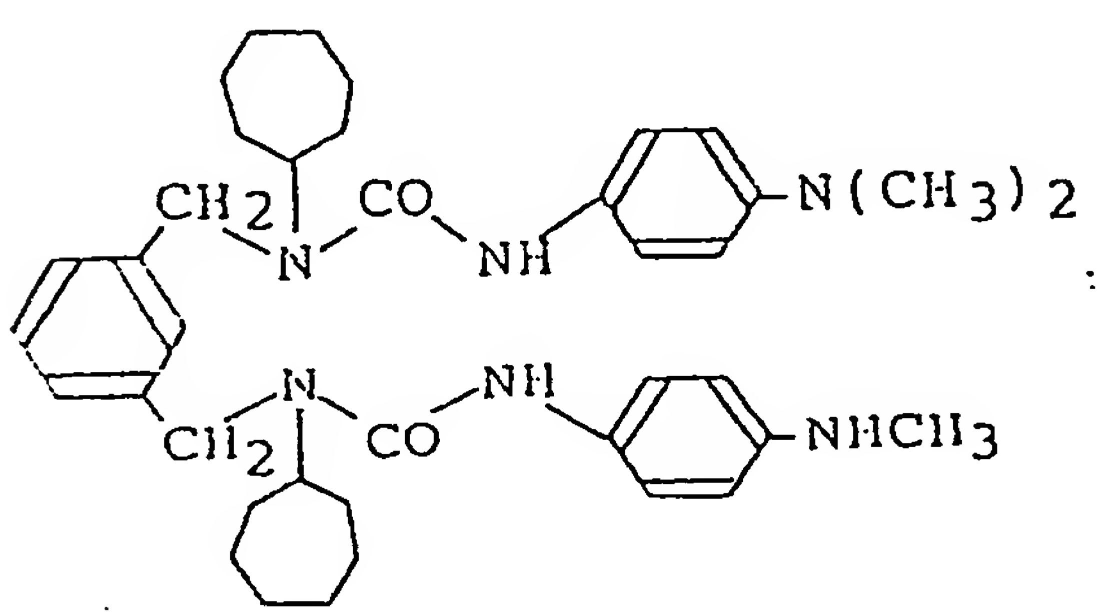


To a solution of 0.47 g 1,3-bis[[3-(p-aminophenyl)-1-cycloheptylureido]methyl]benzene (compound of Example 45) and 0.31 g of 37% formalin in 20 ml ethanol, was added 50 ml of platinum oxide, and the mixture was subjected to catalytic hydrogenation. After a predetermined volume of hydrogen gas was absorbed, the catalyst was filtered off, the solvents were distilled off under reduced pressure from the filtrate, and the residue was purified by silica gel column chromatography, giving 0.37 g of 1,3-bis[[1-cycloheptyl-3-(p-dimethylaminophenyl)ureido]methyl]benzene as amorphous powder. This was treated with ethanolic hydrogen chloride, and the solid thus obtained was recrystallized from ethanol, affording 0.25 g of 1,3-bis[[1-cycloheptyl-3-(p-dimethylaminophenyl)ureido]methyl]benzene dihydrochloride.

(i) M.p. 168-170°C
(ii) Mass (FAB) m/z 653 ($M^+ + 1$)
(iii) Elemental analysis ($C_{40}H_{58}N_6O_2Cl_2$)

	C	H	N
Calcd. (%)	66.19	8.05	11.58
Found (%)	66.21	7.87	11.41

Example 50

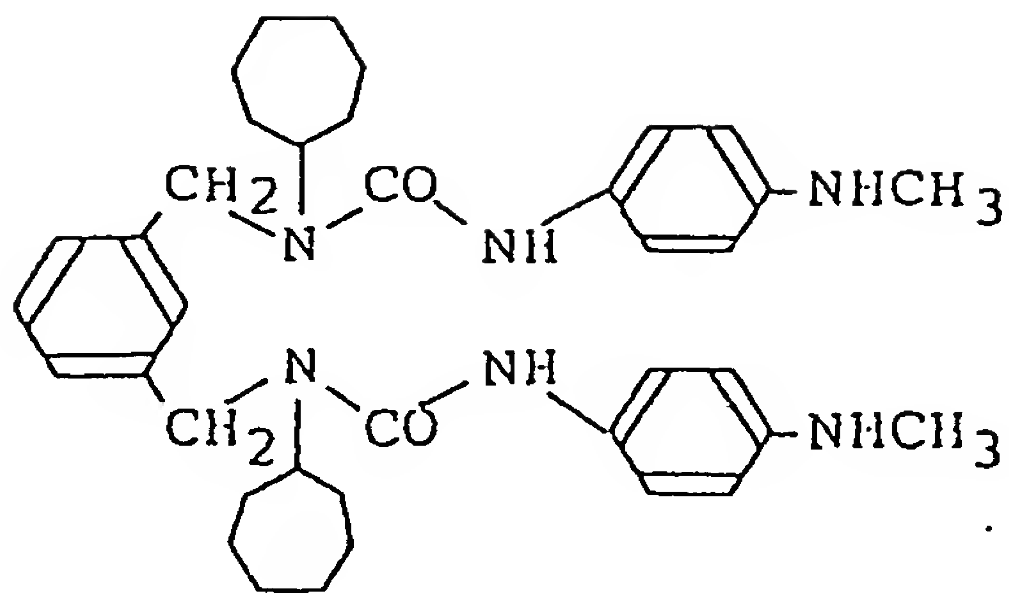


To a solution of 1 g 1,3-bis[[3-(p-aminophenyl)-1-cycloheptylureido]methyl]benzene (compound of Example 45) and 0.29 g of 35% formalin in 50 ml ethanol, was added 100 ml of platinum oxide, and the mixture was subjected to catalytic hydrogenation. After the absorption of hydrogen gas ceased, the catalyst was filtered off, the solvents were distilled off under reduced pressure from the filtrate, and the residue was purified by silica gel column chromatography, giving 0.19 g of 1-[[1-cycloheptyl-3-(p-dimethylaminophenyl)ureido]methyl]-3-[[1-cycloheptyl-3-(p-methylaminophenyl)ureido]methyl]benzene as amorphous powder.

(i) ^{1}H-NMR ($CDCl_3$, δ ppm)
2.74 (3H, s), 2.84 (6H, s), 4.46 (4H, s)
(ii) Mass (FAB) m/z 638 (M^+)
(iii) IR (cm^{-1}), 1648, 1520, 1320, 1240

The following two compounds were prepared in much the same manner as in Example 50.

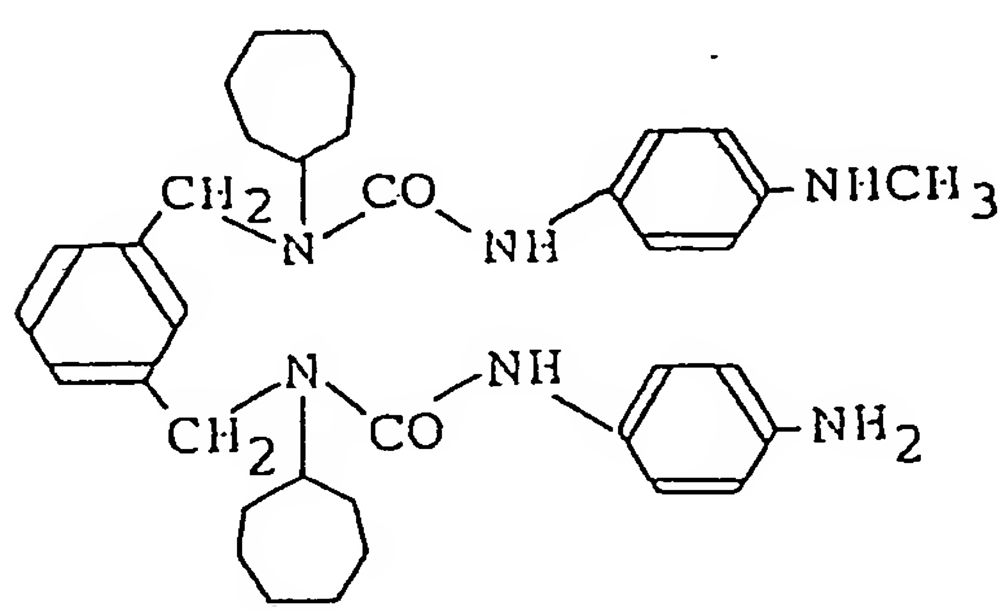
Example 51



1,3-Bis[[1-cycloheptyl-3-(p-methylaminophenyl)ureido]-methyl]benzene

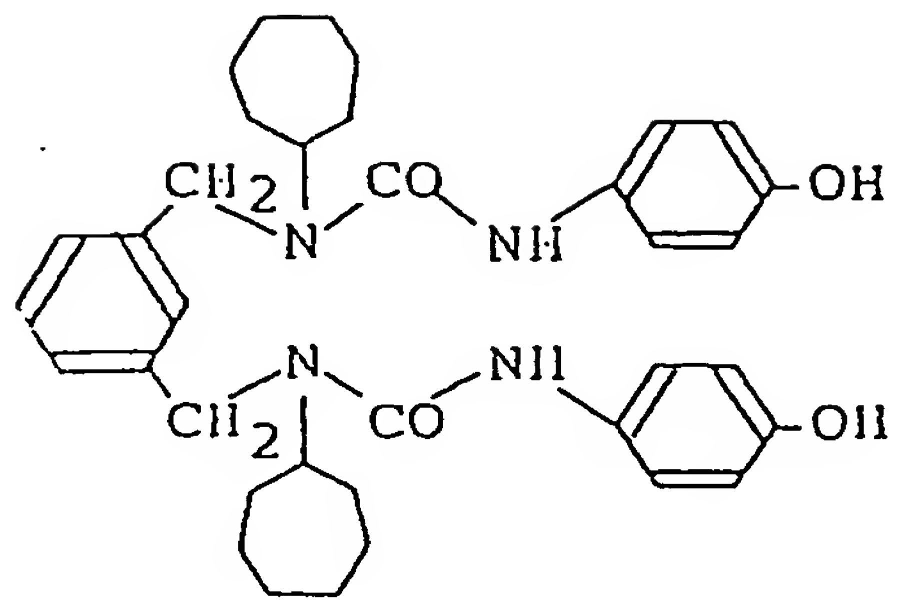
(i) ^{1}H-NMR ($CDCl_3$, δ ppm)
2.76 (6H, s), 4.46 (4H, s), 6.46 (4H, d)
(ii) Mass (FAB) m/z 624 (m$^+$)
(iii) IR (cm^{-1}), 1648, 1522, 1488, 1464

Example 52



1-[[3-(p-Aminophenyl)-1-cycloheptylureido]methyl]-3-[[1-cycloheptyl-3-(p-methylaminophenyl)ureido-]methyl]benzene
(i) ^{1}H-NMR ($CDCl_3$, δ ppm)
2.76 (3H, s), 4.48 (4H, s), 5.92 (2H, s)
(ii) Mass (FAB) 610 (M$^+$)
(iii) IR (cm^{-1}), 1648, 1520, 1238

Example 53



A mixture of 2 g 1,3-bis[[3-(p-acetoxyphenyl)-1-cycloheptylureido]methyl]benzene (compound of Example 44), 30 ml ethanol and 30 ml of 5% aqueous sodium carbonate solution was heated under reflux for ten minutes. After distilling off the ethanol under reduced pressure, water was added to the residue, and the resulting mixture was acidified by addition of concentrated hydrochloric acid under ice cooling. The solid which separated out was collected by filtration and recrystallized from methanol, giving 1 g of 1,3-bis[[1-cycloheptyl-3-(p-hydroxyphenyl)ureido]methyl]benzene.

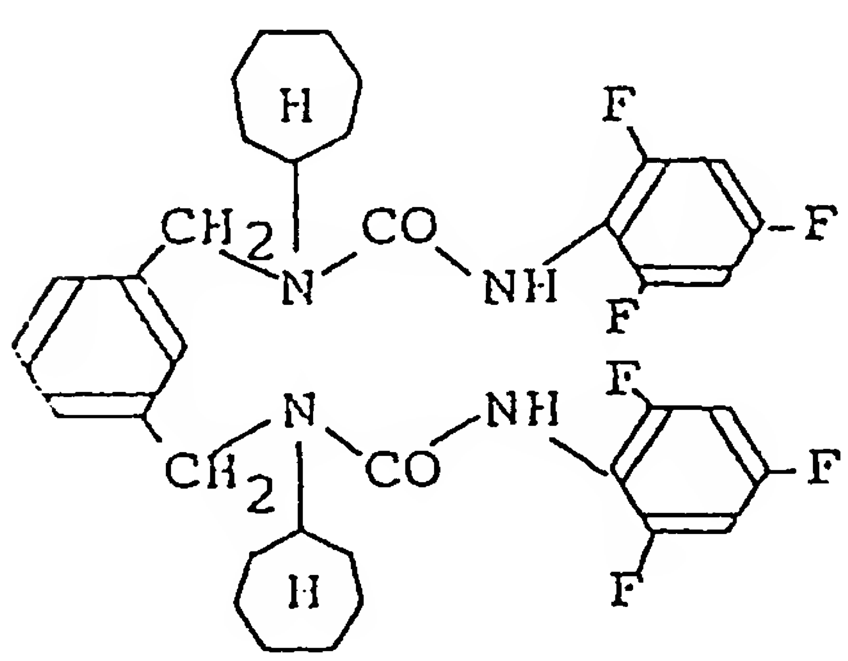
(i) M.p. 230-231°C

(ii) Mass (FAB) m/z 599 ($M^+ + 1$)

(iii) Elemental analysis ($C_{36}H_{46}N_4O_4$)

	C	H	N
Calcd. (%)	72.21	7.74	9.36
Found (%)	72.18	7.72	9.23

Example 54



A mixture of 0.82 g N,N'-dicycloheptyl-m-xylylenediamine, 1.26 g phenyl 2,4,6-trifluorophenylcarbamate and 50 ml toluene was heated under reflux for one hour. After cooling, the reaction mixture was washed twice with 50 ml of 1N-NaOH solution and then with sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure from the dried solution, and the residue was recrystallized from acetone, giving 1.02 g of 1,3-bis[[1-cycloheptyl-3-(2,4,6-trifluorophenyl)ureido]methyl]benzene.

(i) M.p. 107-108°C

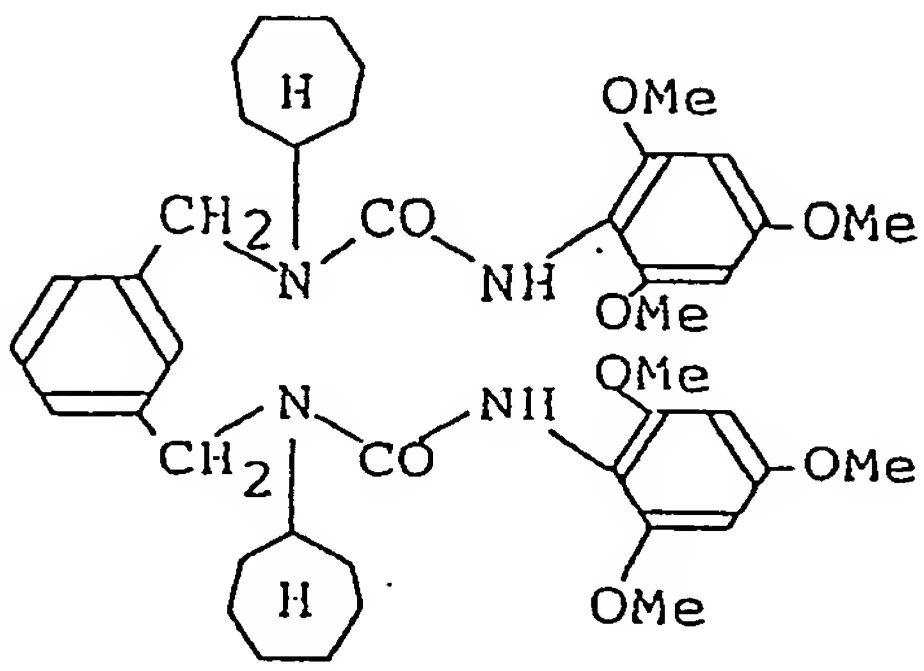
(ii) Mass (FAB) m/z 674 (M^+)

(iii) Elemental analysis ($C_{36}H_{40}N_4F_6O_2$)

	C	H	N
Calcd. (%)	64.08	5.98	8.30
Found (%)	63.88	5.95	8.29

The following compound was prepared in much the same manner as in Example 29.

Example 54

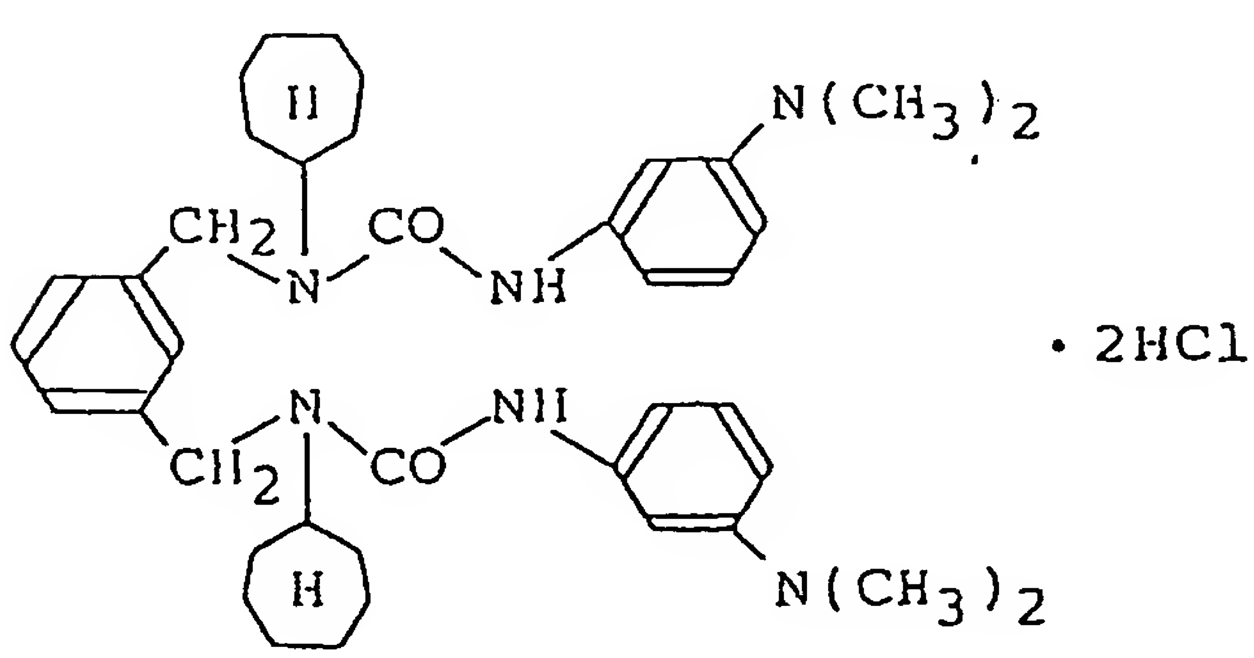


1,3-Bis[[3-(2,4,6-trimethoxyphenyl)-1-cycloheptylureido]-methyl]benzene

(i) M.p. 133-134.5°C
(ii) Mass (FAB) m/z 747 (M^+)
(iii) Elemental analysis ($C_{42}H_{58}N_4O_8$)

	C	H	N
Calcd. (%)	67.54	7.83	7.50
Found (%)	67.07	7.84	7.33

Example 56



To a mixture of 0.50 g 1,3-bis[[3-(m-aminopheny)-1-cycloheptylureido]methyl]benzene (compound of Example 46), 0.17 ml of 35% formalin, 30 ml acetonitrile and 100 ml chloroform, was added with stirring 0.11 g sodium cyanoborohydride at room temperature, and stirring was continued for 20 hours. Sodium cyanoborohydride (0.11 g) and 35% formalin (0.17 ml) were further added, and the mixture was stirred for two hours. Acetic acid (1ml) was then added, and stirring was continued for an additional 30 minutes. The resulting solution was washed with 50 ml of 1N-KOH solution, the aqueous layer was extracted thrice with 100 ml chloroform, and the combined organic solution was washed with aqueous sodium chloride and dried over anhydrous sodium sulfate. The solvents were distilled off under reduced pressure from the dried solution, and the residue was purified by silica gel column chromatography, followed by treatment with ethanolic hydrogen chloride. Distilling off the solvent gave 0.25 g of 1,3-bis[[1-cycloheptyl-3-(m-dimethylaminophenyl)ureido-]methyl]benzene dihydrochloride as amorphous powder.

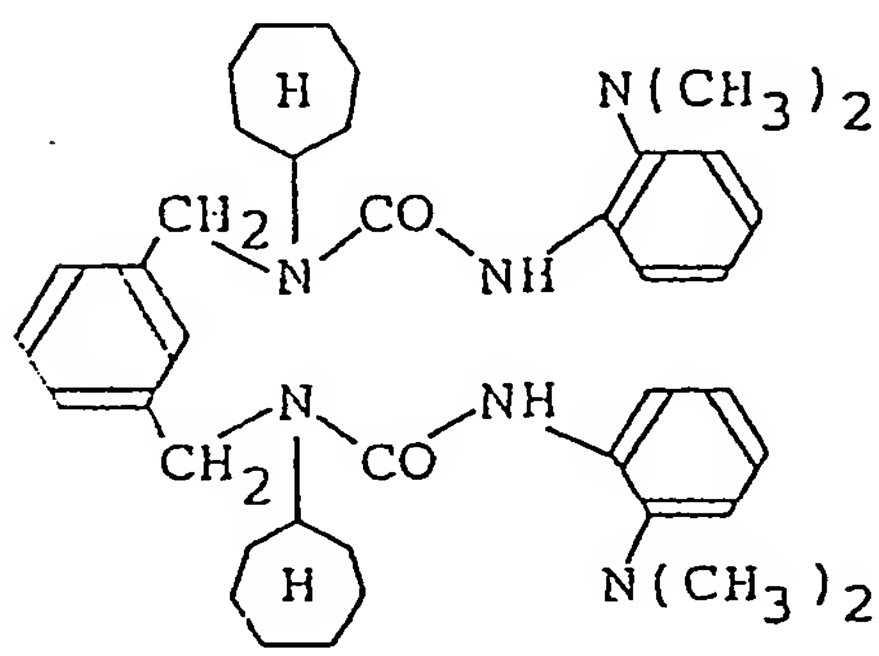
(i) ^{1}H-NMR (DMSO-d_6, δ ppm)

3.13 (12H, s), 4.59 (4H, s)

(ii) Mass (FAB) 653 (M^{+} + 1)

(iii) IR (cm^{-1}), 2936, 1654, 1540, 1464

Example 57



To a mixture of 0.6 g 1,3-bis[[3-(o-aminophenyl)-1-cycloheptylureido]methyl]benzene (compound of Example 47), 0.43 ml of 35% formalin, 50 ml acetonitrile and 50 ml benzene, was added with stirring 0.12 g sodium cyanoborohydride at room temperature, and stirring was continued for two hours. Sodium cyanoborohydride (0.12 g) and 35 formalin (0.43 ml) were further added, and the mixture was stirred for two hours. Acetic acid (1ml) was then added, and stirring was continued for an additional 30 minutes. The solvents were distilled off from the reaction mixture, and 50 ml of 1N-KOH solution was added, followed by extraction with 50 ml chloroform three times. The extract was washed with saturated aqueous sodium chloride and dried over anhydrous potassium carbonate. The solvent was distilled off under reduced pressure from the dried solution, and the residue was purified by silica gel column chromatography and then recrystallized from acetone, giving 0.16 g of 1,3-bis[[1-cycloheptyl-3-(o-dimethylaminophenyl)ureido]methyl]benzene dihydrochloride.

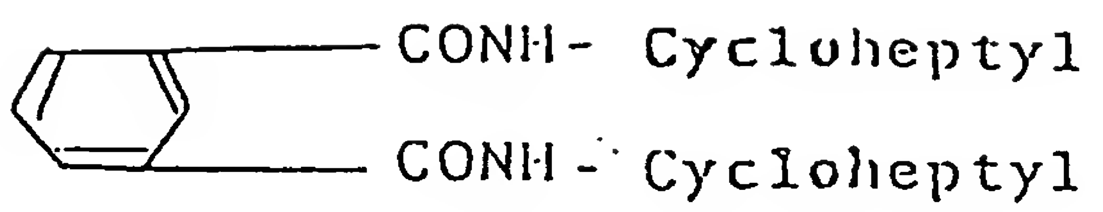
(i) M.p. 159-160°C

(ii) Mass (FAB) m/z 653 (M^{+})

(iii) Elemental analysis ($C_{40}H_{56}N_6O_2$)

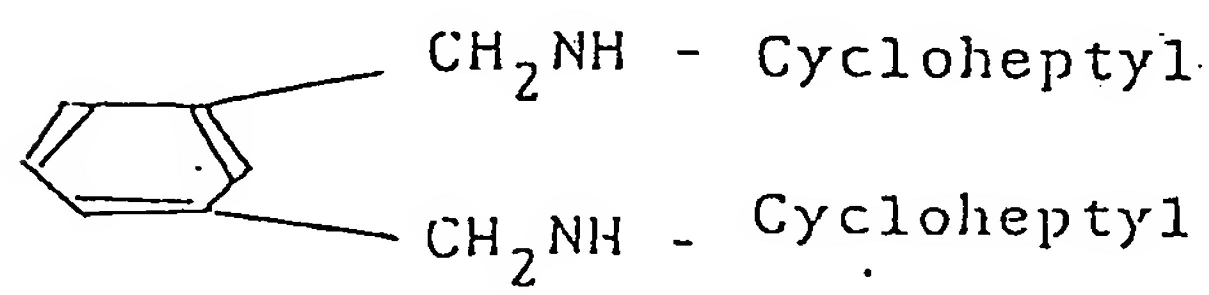
	C	H	N
Calcd. (%)	73.58	8.64	12.87
Found (%)	73.42.	8.75	12.76

Reference Example 10



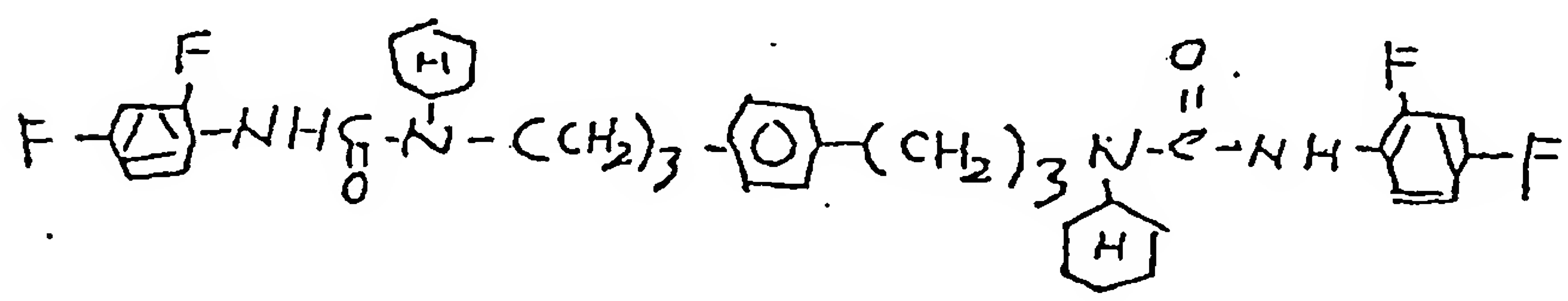
20.8 g of cycloheptylamine and 20.25 g of triethylamine were dissolved in 500 ml of methylenechloride, and then 17.0 g of iso-phthaloyl chloride was added to thereto. The mixture was stirred at room temperature for 2 hours, 500 ml of water was added, then conc. HCl was added thereto while stirring . Precipitated material was collected by filtration, washed with methylene chloride and water successively, and dried giving 28.7 g of N,N'-dicycloheptylisophthalamide.
mp. 285-286°C
IR (cm^{-1}): 3264, 1648, 1632, 1560
Mass (m/z): 356 (M^+)

Reference Example 11 (Starting material in Example 1 and other Examples)



24.3 g of N,N'-dicycloheptylisophthalamide (obtained in Reference Example 10) was suspended in 500 ml of toluene, and 96 ml of toluene solution (70%) containing bis(2-methoxyethoxy)aluminum sodium hydride was added thereto dropwise while stirring at room temperature. The mixture was refluxed for 3 hours, and 400 ml of 2.5N aqueous sodium hydroxide was added thereto portionwise. The toluene layer was separated and collected, washed with saturated aqueous NaCl, and dried. The solution was removed by distillation, giving 22.3 g of N,N-dicycloheptyl-m-xylenediamine.
^{1}H-NMR ($CDCl_3$, δ ppm): 3.74 (4H, s), 7.08-7.36 (4H, m),
IR (cm^{-1}): 2936, 2860, 1462, 1114
Mass (FAB) m/z 329 (M^++1)

Example 58



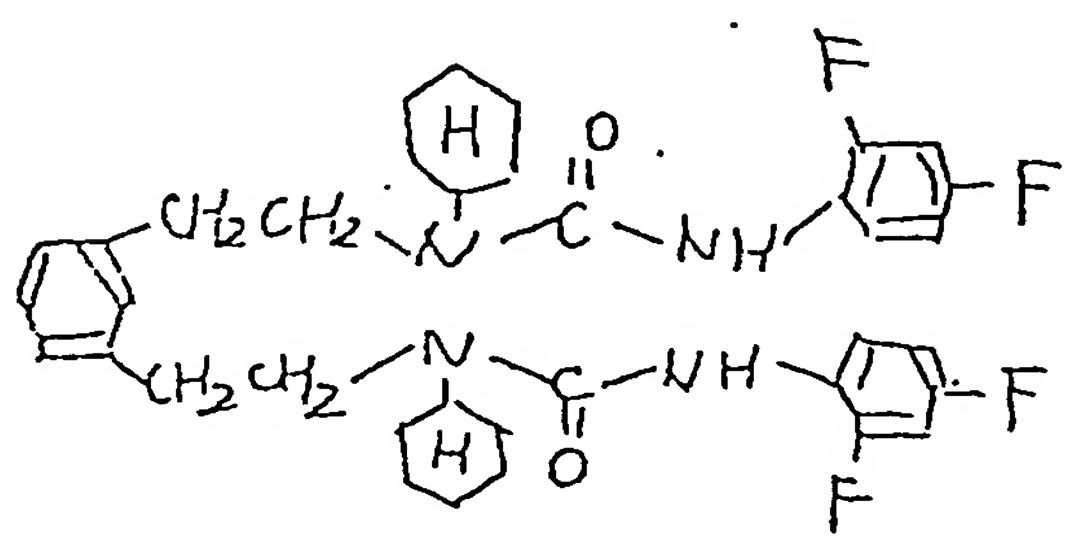
1,4-bis[[1-cyclohexyl-3-(2,4-difluorophenyl)ureido]-propyl]benzene

The above compound was prepared in much the same manner as in Example 14.
(i) M.p. 76-78°C
(ii) ^{1}H-NMR ($CDCl_3$, δ ppm)
2.14 (4H, t), 3.20 (4H, t), 6.26 (2H, d)

(iii) Elemental analysis ($C_{38}H_{46}N_4O_2F_4$)

	C	H	N
Calcd. (%)	68.45	6.95	8.40
Found (%)	68.66	7.13	8.22

Example 59



1,3-bis[[1-cyclohexyl-3-(2,4-difluorophenyl)-uréido]ethyl]benzene

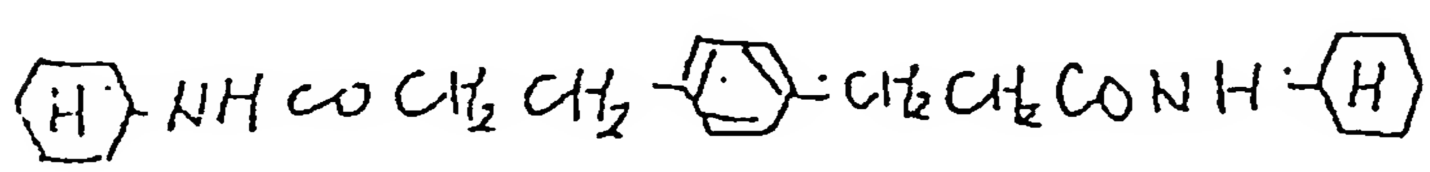
The above compound was prepared in much the same manner as in Example 1.

(i) ^{1}H-NMR ($CDCl_3$, δ ppm)

2.88 (4H, t), 3.32 (4H, t), 6.38 (2H, d)

(ii) IR (cm^{-1}) 2944, 1654, 1522, 1432

Reference Example 12

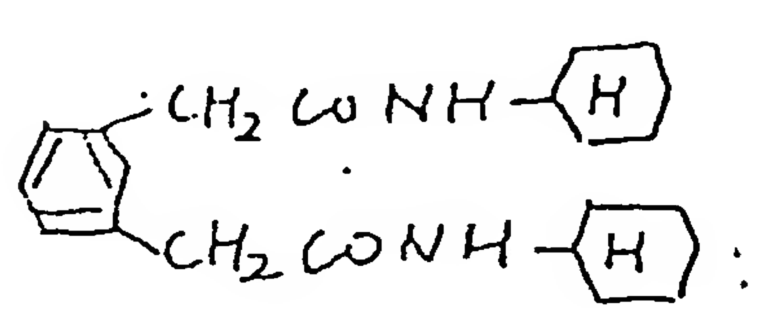


To a solution of 4.9 g of cyclohexylamine and 5.4 g of triethylamine in 100 ml of methylenechloride, was added 5.8 g of 1,4-phenylenedipropionyl choride under ice cooling with stirring. Stirring was continued for 3 hours at room temperature, and 500 ml of water was added to the reaction solution. Conc. HCl was added to the mixture until the aqueous layer became weakly acidic. The solid material precipitated was collected by filtration, washed with methylenechloride and water in that order, and dried, giving 7.4 g of N,N'-dicyclohexyl-1,4-phenylenedipropionamide.

(i) M.p. 267-269°C

(ii) IR (cm^{-1}) 3312, 1642, 1548

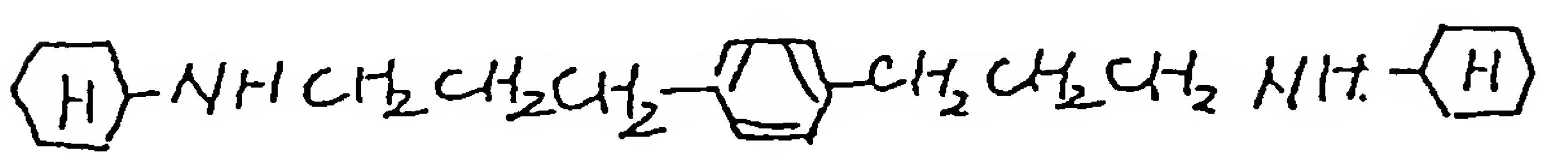
Reference Example 13



N,N-dicyclohexyl-1,3-phenylenediacetamide

(i) M.p. 221-222° C
(ii) IR (cm^{-1}) 3304, 2944, 1646, 1550

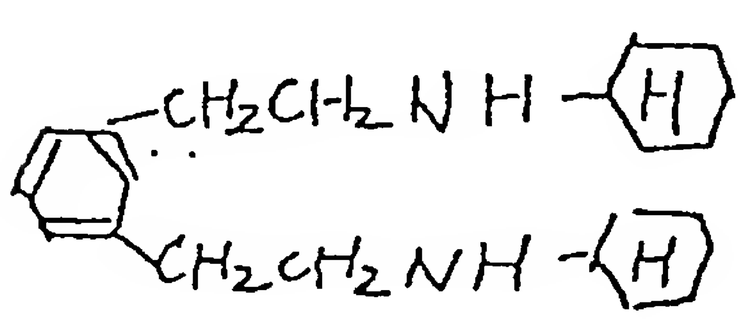
Reference Example 14 (Starting material for Example 58)



1.5 g of N,N'-dicyclohexyl-1,4-phenylenedipropionamidewas added to 20 ml of dry tetrahydrofuran, and after adding thereto dropwise 2.4 ml of borandimethyl sulfide complex under ice cooling, the mixture was refluxed under heating for 4 hours. After adding to the mixture 0,33 ml of methanol under ice cooling and stirring the mixture for 30 minutes at room temperature, 2 ml of conc.-HCl was added to the mixture under ice cooling. The mixture was refluxed for 30 minutes. The reaction solution was ice-cooled, and the solid material precipitated was collected by filtration and washed with ether. The solid material thus obtained was dissolved in chloroform, and the solution was alkalified with aqueous NaOH. The chloroform layer was dried, and the solvent was distilled away under reduced pressure, giving 1.3 g of N,N'-dicyclohexyl-1,4-phenylenedipropylamine.

(i) ^{1}H-NMR ($CDCl_3$, δ ppm)
7.12 (4H, s)
(ii) IR (cm^{-1}) 2936, 2856, 1516, 1452
(iii) Mass spectrum (EI) m/z 356 (M^+)

Reference Example 15 (Starting material for Example 59)



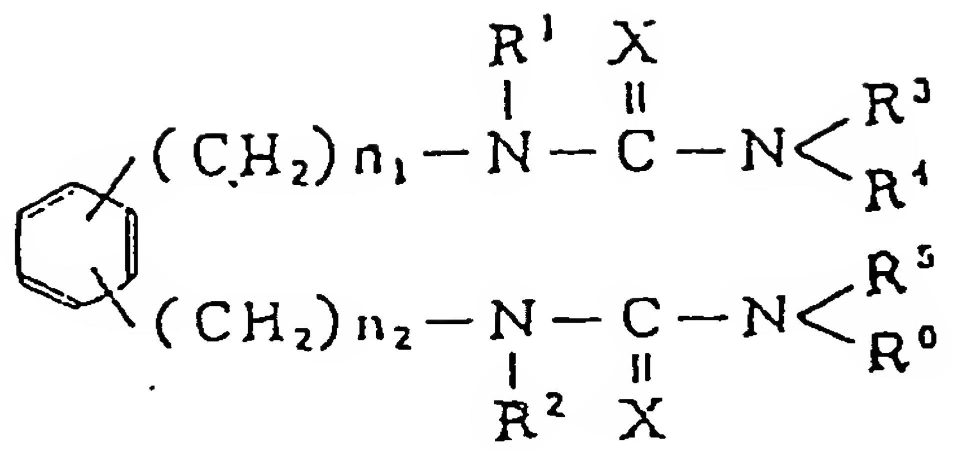
N,N-dicylcohexyl-1,3-phenylenediethylamine

The above compound was prepared in much the same manner as in Reference Example 14.

(i) ^{1}H-NMR ($CDCl_3$, δ ppm)
2.90 (8H, t)
(ii) IR (cm^{-1}) 2936, 2856, 1452, 1130

Claims

A compound of formula (I) or a salt thereof:



(I)

wherein R^1 and R^2 are the same or different and selected from alkyl and cycloalkyl groups and C_1-C_5 alkyl groups substituted by cycloalkyl; R^3, R^4, R^5 and R^6 are the same or different and selected from a hydrogen atom and C_1-C_5 alkyl, cycloalkyl, aralkyl, pyridyl, and phenyl groups; X is an oxygen or sulfur atom; and n_1 and n_2 are the same or different integers of 1 to 6.

2. A compound according to claim 1 wherein R^1 and R^2 are cycloalkyl groups; R^3 and R^5 are the same or different phenyl groups; R^4 and R^6 are the same or different and selected from a hydrogen atom and C_1-C_5 alkyl, cycloalkyl, aralkyl, pyridyl, and phenyl groups; n_1 and n_2 are integers of 1 to 3.

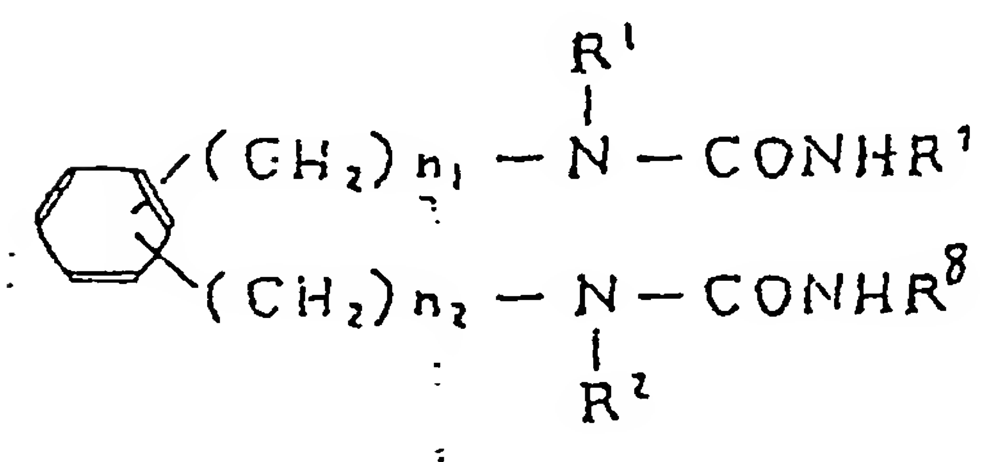
3. A compound according to claim 1 or 2 wherein at least one said phenyl groups is substituted, preferably by one or more substituents selected from C_1-C_5 alkyl, halogeno-(C_1 -C_5 alkyl), halogen, nitro, amino, mono- and di-(C_1-C_5 alkyl) amino, (C_1-C_5 acyl)amino, hydroxyl, C_1-C_5 alkoxy and C_2-C_5 acyloxy.

4. A compound according to claim 1 which 1,3-bis[(1-cycloheptyl-3-(2,4-difluorophenyl)-ureido)methyl-]benzene or a salt thereof.

5. A compound according to claim 1 which is 1,3-bis[(1-cycloheptyl-3-(p-dimethylaminophenyl)-ureido)methyl]benzene or salt thereof.

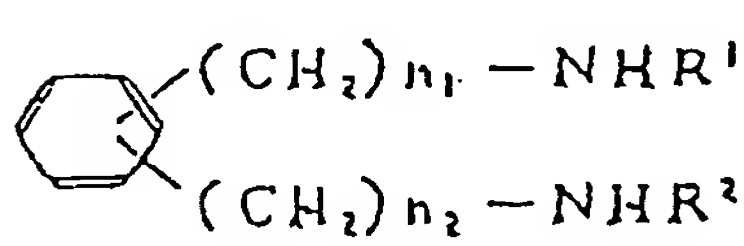
6. A medical composition containing as an active component a compound or pharmaceutically acceptable salt according to any of claims 1 to 5.

7. A process for producing a compound (Ia)



(Ia)

which comprises reacting compound (II)



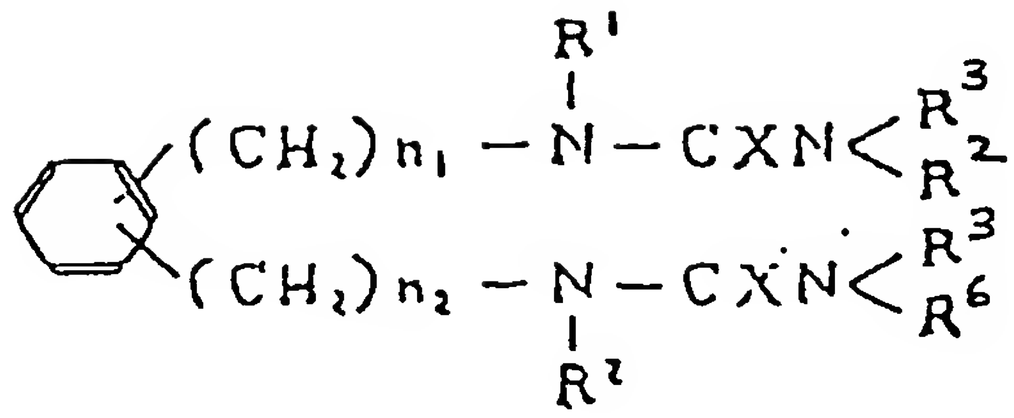
(II)

with compound(s) (III)

R^7NCX (and/or R^8NCX) (III)

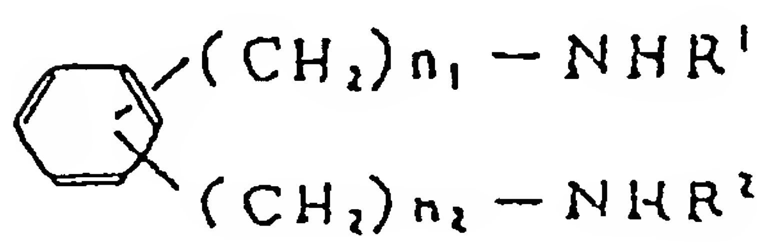
and optionally converting the product to or from salt form, wherein R^1, R^2, X, n_1 and n_2 are as defined in claim 1, 2 or 3 and R^7 and R^8 are as defined for R^3 to R^6 in claim 1, 2 or 3.

8. A process for producing a compound (I)



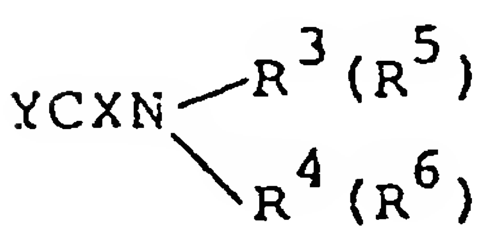
(I)

which comprises reacting compound (II)



(II)

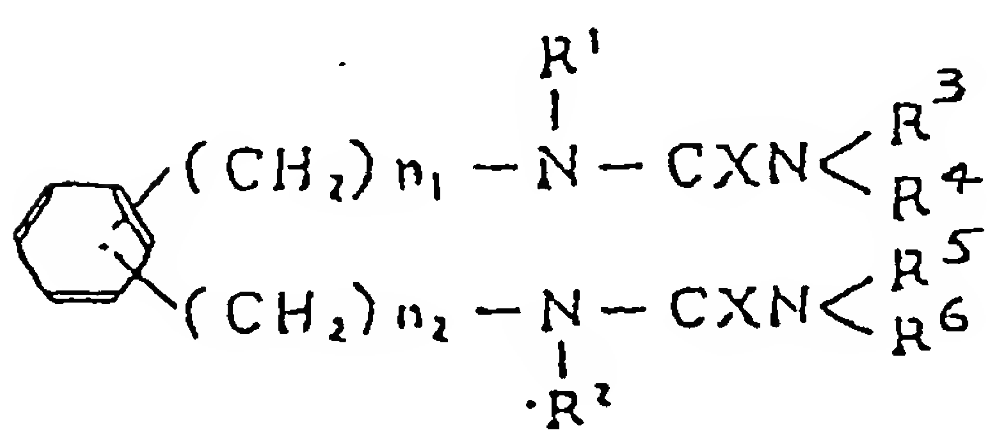
with compound(s) (IV)



(IV)

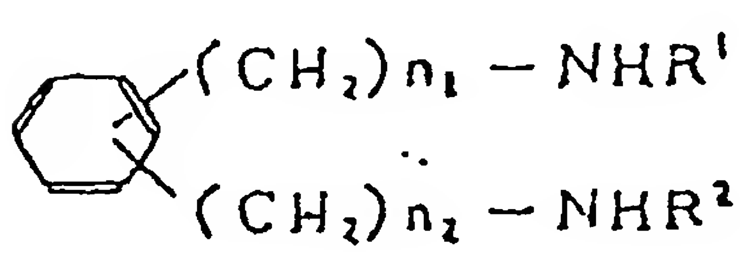
and optionally converting the product to or from salt form, wherein R^1 to R^6, X, n_1 and n_2 are as defined in claim 1, 2 or 3 and Y is halogen.

9. A process for producing a compound (I)



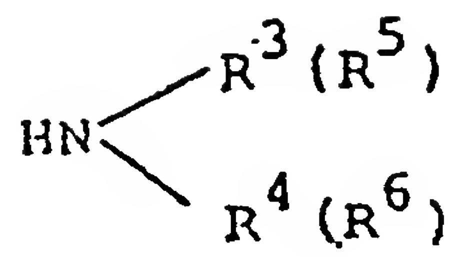
(I)

which comprises reacting compound (II),



(II)

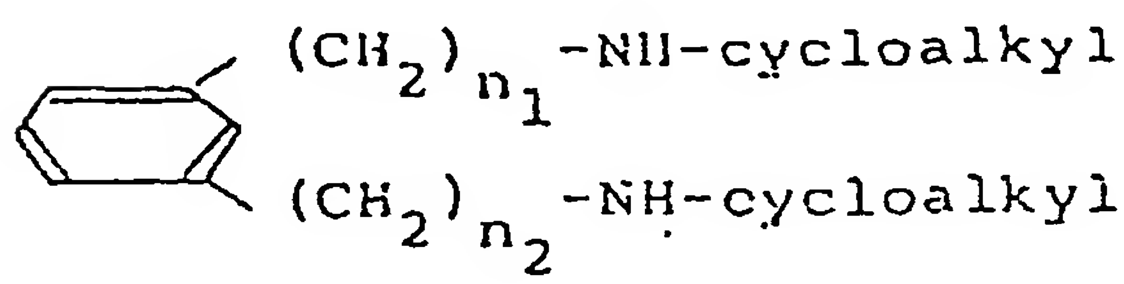
Y-CXO-R^9, and compound(s) (VIII)



(VIII)

and optionally converting the product to or from salt form, wherein R^1 to R^6, X, n_1 and n_2 are as defined in claim 1, 2 or 3 and R^9 represents C_1-C_5 alkyl or a phenyl group.

10. An intermediate compound of the following formula:



wherein n_1 and n_2 are the same or different integers of 1 to 6.

European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 89300380.6

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	EP - B1 - 0 000 376 (NIHON TOKUSHU NOYAKU SEIZO) * Claims 1,2 * --	1,7	C 07 C 127/19 C 07 C 127/17 C 07 C 157/09 C 07 C 157/07 C 07 C 87/455 A 61 K 31/17
A	EP - A2 - 0 072 528 (BAYER) * Claims 1,3,4 * --	1,7,10	
A	US - A - 4 460 602 (BRIAN L. BUCKWALTER et al.) * Abstract * --	1,6	
X	DE - B - 1 942 877 (SHOWA DENKO) * Table; compound 12 * --	10	
X	CHEMICAL ABSTRACTS, vol. 74, no. 23, June 7, 1971, Columbus, Ohio, USA BERGMANN, ERNST D et al. "Synthesis and properties of some phosphorusaziridinyl compounds" page 441, abstract no. 125 293g in connexion with Chem. Abstr. Collective Index, vol. 66-75, page 7290 F, $C_{18}H_{28}N_2$, last compound & J.Polym.Sci., Part C, 1970, No. 31, 375-97 ----	10	TECHNICAL FIELDS SEARCHED (Int. Cl.4) C 07 C 127/00 C 07 C 157/00 C 07 C 87/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	03-04-1989	REIF

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
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P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document